11. 12. 9

23

April 1989 Vol 61 No 4

British Heart Journal

A monthly journal of cardiology published in association with the British Cardiac Society

CVK-H06005-23-P25739

Review: Does the atrioventricular node conduct? *F L Meijler, C Fisch* **309**

A double blind placebo controlled study of early and late administration of recombinant tissue plasminogen activator in acute myocardial infarction *A J McNeill, S R Cunningham, D J Flannery, G W N Dalzell, C M Wilson, N P S Campbell, M M Khan, G C Patterson, S W Webb, A A J Adgey* **316**

Impact of a policy of direct admission to a coronary care unit on use of thrombolytic treatment *J M A Burns, K J Hogg, A P Rae, W S Hillis, F G Dunn* **322**

Use of a hollow wire to facilitate angioplasty of occluded vessels *L D R Smith, D Katritsis, M M Webb-Peploe* **326**

Effect of flosequinan on exercise capacity and symptoms in severe heart failure *J S Elborn, C F Stanford, D P Nicholls* **331**

Half time of the diastolic aortoventricular pressure difference by continuous wave Doppler ultrasound: a measure of the severity of aortic regurgitation? *S O Samstad, L Hegrenaes, T Skjaerpe, L Hatle* **336**

Transmitral velocities measured by pulsed Doppler in healthy volunteers: effects of acute changes in blood pressure and heart rate *S A Smith, J E Stoner, A E Russell, J M Sheppard, P E Aylward* **344**

Isoprenaline as an aid to the induction of catecholamine dependent supraventricular tachycardias during programmed stimulation *B Brembilla-Perrot, A Terrier de la Chaise, M Pichené, E Aliot, F Cherrier, C Pernot* **348**

Endocarditis in intravenous drug abusers with staphylococcal septicaemia *J M A Burns, K J Hogg, W S Hillis, F G Dunn* **356**

Aortic valvotomy for critical aortic stenosis in neonates and infants aged less than one year *S Balaji, B R Keeton, G R Sutherland, D F Shore, J L Monro* **358**

Diagonal earlobe creases and fatal cardiovascular disease: a necropsy study *N Kirkham, T Murrells, D H Melcher, E A Morrison* **361**

Case reports

- Perinatal management of critical aortic valve stenosis diagnosed by fetal echocardiography *M A Robertson, P J Byrne, P A Penkoske* **365**
- Wolff-Parkinson-White syndrome after transplantation of the heart *J-J Goy, L Kappenberger, M Turina* **368**
- Serial angiographic findings during the development of a saccular aneurysm of the coronary artery in association with unstable angina *J Goudevenos, M Been, D Williams* **372**
- Unruptured aneurysm of the sinus of Valsalva presenting with isolated heart block: echocardiographic diagnosis and successful surgical repair *R A S Ahmad, S Sturman, R D S Watson* **375**
- Propranolol induced bradycardia in tetralogy of Fallot *D J Clark, K C Chan, J L Gibbs* **378**

Notices **380**

British Medical Association

ASTM CODEN: BHJUAV 61(4) 309–380 (1989)
ISSN 0007-0769

British Heart Journal

P, 25739

EDITOR Dennis Krikler ASSISTANT EDITORS M J Davies, Kim Fox, Peter Mills

EDITORIAL COMMITTEE
Clive P Aber Kate Bull Keith Dawkins Alan B Houston Barry R Keeton Michael Marmot
Alexander L Muir Paul J Oldershaw Philip A Poole-Wilson David B Shaw
Tom Treasure David E Ward John Watkins Peter Wilde
Editor: *British Medical Journal* Editor: *Cardiovascular Research*

TECHNICAL EDITOR Jane Dawson EDITORIAL ASSISTANT Anne Oliver
STATISTICAL ADVISER Stephen J W Evans

Notice to contributors

Papers relating to the heart and circulation should be sent in triplicate to the Editor, British Heart Journal, BMA House, Tavistock Square, London WC1H 9JR, and be prepared according to the *Uniform requirements for manuscripts submitted to biomedical journals* (Vancouver agreement) (*Br Med J* 1988;**296**:401–5). Authors are asked to complete a copy of the checklist provided (1988;**59**:47 (January issue)) when submitting their manuscripts for publication. The reference number given on the acknowledgement postcard sent out by the editorial office should be quoted on all subsequent correspondence and telephone inquiries. A covering letter must be signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. All authors will be required to transfer copyright of their articles to the journal before publication. (All material for possible publication (including Letters to the Editor) *must* be typed in *double spacing* with 4 cm margins.)

Ethical standards
Authors are expected to comply with the code of ethics known as the Declaration of Helsinki. Where appropriate, manuscripts should include a statement that the research protocol has been approved by the locally appointed ethics committee and that the informed consent of the subjects has been obtained.

Case reports should convey only the essential facts of a case and the discussion and bibliography be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and include no more than two Figures.

Abbreviations should *not* be used in the text, except for mathematical calculations and units of measurement.

References must be cited precisely according to the Vancouver agreement and be typed in *double spacing*. As a general rule, no more than three references should be cited for any one statement.

Authors are responsible for the accuracy of any references cited: these should be checked at source or with the listing in Index Medicus.

Units of measurement
All haematological and clinical chemistry measurements should be given as SI units. Blood pressures should be given in mm Hg. Measurements of length, height, weight, and volume should be reported in metric units and temperatures should be reported in degrees Celsius.

Tables must be typed on separate sheets and not in the text. Titles should be provided, and all abbreviations used must be given in full in a footnote.

Illustrations (for general requirements, please refer to *Br Heart J* 1984; **51:** 1–6).

Electrocardiograms: Black and white prints only should be sent and not the original tracings. If several tracings are grouped in a single Figure only a few complexes should be shown; the width should not exceed 14 cm unless a reduction in scale is possible.

Echocardiograms: Since these will be reproduced at a width of 7 cm or less all unnecessary or irrelevant detail (such as electronic writing) should be removed. Labelling must be superimposed directly on to the print itself and only where essential be shown on an accessory drawing. Echocardiograms obtained with 30° sector scans or bistable equipment or recorded on ultraviolet paper are not suitable for publication.

Figure legends must include an explanation of all abbreviations used in the Figure.

Copyright permission to reproduce material published elsewhere must be obtained in writing and acknowledged in the manuscript.

Proofs of articles accepted for publication will be sent for the author's approval. Proof corrections should be kept to a minimum.

Notice to subscribers

British Heart Journal is published monthly. The annual subscription rates are £97.00 inland and £113.00 overseas (USA $182·00). Combined rate: *British Heart Journal* and *Cardiovascular Research* £184 inland and £214 overseas (USA $350·00). Orders should be sent to The Subscription Manager, *British Heart Journal*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card. (For the convenience of readers in the USA subscription orders ($182) with or without payment may also be sent to British Medical Journal, Box 560B, Kennebunkport, Maine 04046. All inquiries, however, must be addressed to the Publisher in London.) **All copies are despatched by air-speed.** First class rates available on request.

COPYRIGHT © 1989 by the *British Heart Journal*. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission of the *British Heart Journal*.

Second class postage paid, Rahway NJ Postmaster: send address changes to: British Heart Journal c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

Br Heart J 1989;61:309–15

Review

Does the atrioventricular node conduct?

FRITS L MEIJLER,* CHARLES FISCH†

*From the *Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands and the †Indiana University School of Medicine, Krannert Institute of Cardiology, Indianapolis, USA*

It is difficult to be certain when the term "conduction" was first applied to the transfer of atrial activation to the ventricles.[1] In 1894, Engelmann used the word "Leitung", which can be translated as "connection" or as "conduction".[2] In 1906, Tawara described the atrioventricular node, which he termed "Das Reizleitungssystem des Herzens".[3] The mechanism of atrioventricular transmission continued to be a subject of considerable debate.[4-9] There is a summary of the various mechanisms that were thought to explain atrioventricular transmission in Scherf and Cohen's book on the atrioventricular node.[10] Primarily through the work of Hoffman and Cranefield and their associates,[11 12] and to a lesser extent others,[13 14] it became generally accepted that atrial excitation was slowly "conducted" through the atrioventricular node to the His-Purkinje system and the ventricular myocardium.

Hoffman and Cranefield stated that "the excitable cell . . . possesses the same electrical properties as a telegraph cable".[15] Because the "connecting" tissue between the atria and the ventricles was regarded as a series of excitable cells, it followed that the atrioventricular junction was a conduction system. None the less, studies of the complicated structure of the mammalian atrioventricular junction,[14] and the time relation between recorded action potentials from exposed rabbit atrioventricular node[16 17] have not as yet yielded sufficient data to construct a model of the spatial excitation of the atrioventricular node that is analogous to that of the canine and human ventricles.[18 19] The atrioventricular node cannot be mapped with the preciseness required to document the sequence of excitation through this part of the specialised conduction system. Although it seems logical to assume conduction through the atrioventricular node, this claim remains open to question and conjecture. Moreover, some observations[20] suggest that the traditional concept of the atrioventricular junction as a passive cable with varying electrical properties warrants further examination. The concept of the atrioventricular node as an oscillator—that is an unprotected pacemaker—may be a somewhat more flexible and biologically sound explanation of the linear and the non-linear functions of the atrioventricular junction.[21]

The concept of the atrioventricular node as an unprotected pacemaker is not new. In 1925, Lewis[22] in referring to the work of Mackenzie[23] and Mobitz,[24] stated that, "The structure of the A-V node, and its similarity to the S-A node, has suggested the last as the ventricular pacemaker, and it has been thought that a new and distinct wave may start in this after each systole of the auricle".

Functions of the atrioventricular node

A reasonable starting point from which to consider the possibility of the atrioventricular node as an unprotected pacemaker or oscillator is to examine its three functions: (*a*) synchronisation of atrial and ventricular contraction with appropriate and variable delay depending on the heart rate,[25] under conditions of varying autonomic nervous system influences and in different species,[26 27] (*b*) protection of the ventricles from excessive atrial rates when there is atrial arrhymia,[28 29] and (*c*) the role as a latent escape pacemaker in the event of atrioventricular block or atrial bradycardia or arrest.[30]

The atrioventricular node can act as a passive pacemaker and deductive reasoning supports the concept of the atrioventricular node as an electrotonically modulated pacemaker during atrial fibrillation.[20] So the question arises as to whether the atrioventricular node, in addition to its pacemaker function, needs to act as a conduit with varying resistive and capacitive properties[15] to perform the three functions or can all functions of the atrioventricular node be explained on the basis of the assumed pacemaker characteristics?

Atrioventicular node as an oscillator (pacemaker)

In 1929 Van der Pol and Van der Mark proposed that the heart beat could be viewed as a relaxation oscillator.[31] In 1940 Bethe suggested that other

Requests for reprints to Professor Frits L Meijler, Interuniversity Cardiology Institute of the Netherlands, POB 19258, 3501 DG Utrecht, The Netherlands.

rhythmic phenomena of the heart, such as a bigeminal rhythm, should also be regarded as oscillatory movements.[32] A relaxation oscillator is best described as a condenser that is periodically discharged by the ignition of a neon tube. The frequency of a relaxation oscillator is dependent on the energy supplied and can be increased or decreased by certain external periodic electrical phenomena of small amplitude, such as a sine wave current. In 1973 Van der Tweel *et al* showed that the sinus node of an isolated rat heart could be synchronised the same way as a relaxation oscillator.[33] These observations strongly support the notion that cardiac pacemaker cells may behave, in a physical sense, like relaxation oscillators and, apart from its intrinsic firing rate, the atrioventricular node may not be so different from the sinoatrial node.[34] Grant first suggested that the atrioventricular node can be regarded as an oscillator.[21] Subsequent studies supported this concept.[35 36] More recently Schamroth *et al* presented evidence that an ectopic pacemaker may be regarded as an oscillator that is synchronised (entrained) by the electrotonic modulation generated by the sinus impulse.[37]

ATRIAL FIBRILLATION

In 1983 Cohen *et al* developed a quantitative model for the ventricular response during atrial fibrillation.[38] In this model the atrioventricular junction is regarded as the equivalent of a single pacemaker cell characterised by a refractory period and spontaneous phase 4 depolarisation. In 1986 Van der Tweel and co-workers provided experimental evidence that the atrioventricular node may indeed act as a periodically perturbed biological oscillator.[39]

If we assume that the atrioventricular node acts as an oscillator, can its functions, outlined above, be served and its role in control of cardiac rhythmicity be explained? It is reasonable to assume that the random ventricular rhythm during atrial fibrillation can be the result of electrotonic modulation of phase 4 of the transmembrane action potential[20 38] of the atrioventricular node by randomly spaced atrial excitations.[40-42] Instead of postulating concealed conduction of atrial impulses into the atrioventricular junction[43-45] during atrial fibrillation, let us assume that, depending on the random strength, direction, and timing, the electrotonic effect of the atrial excitation either accelerates diastolic depolarisation of the atrioventricular nodal pacemaker (and thus shortens the RR interval) or decelerates the diastolic depolarisation (hyperpolarise) (and thus lengthens the RR interval) (fig 1). In such a model the ventricular rate and rhythm during atrial fibrillation

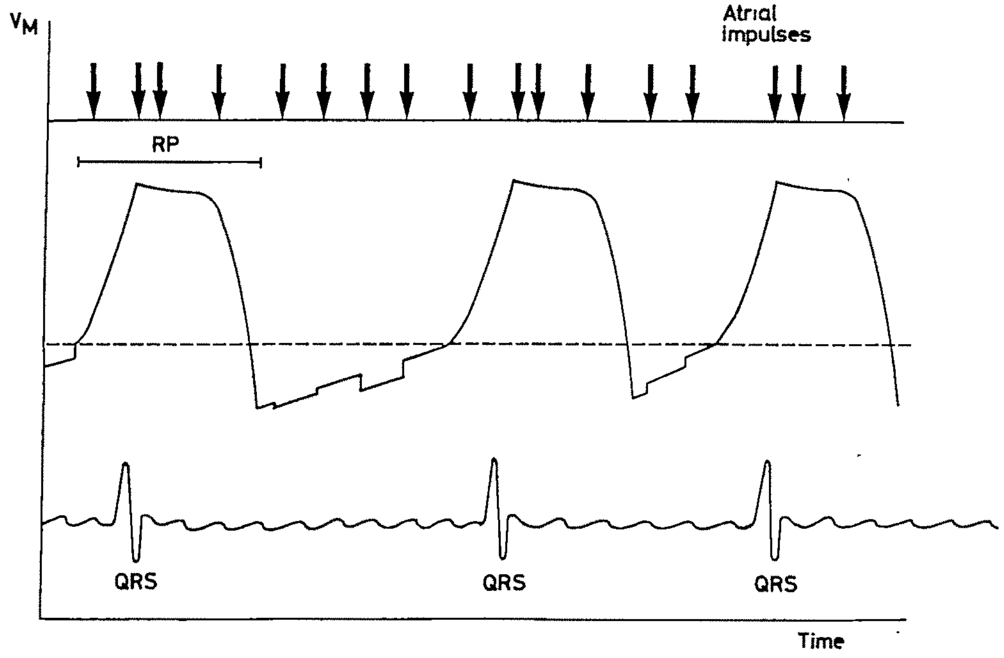


Fig 1 *Hypothetical model of the atrioventricular nodal pacemaker during atrial fibrillation. Depending on strength, timing, and direction of the atrial impulses, diastolic depolarisation can be speeded up or slowed down (hyperpolarisation) during atrial fibrillation. This explains why the RR intervals vary randomly. This model is an extension of the model of Cohen et al.*[38]*; RP, refractory period; VM, voltage of hypothetical monophasic action potential.*

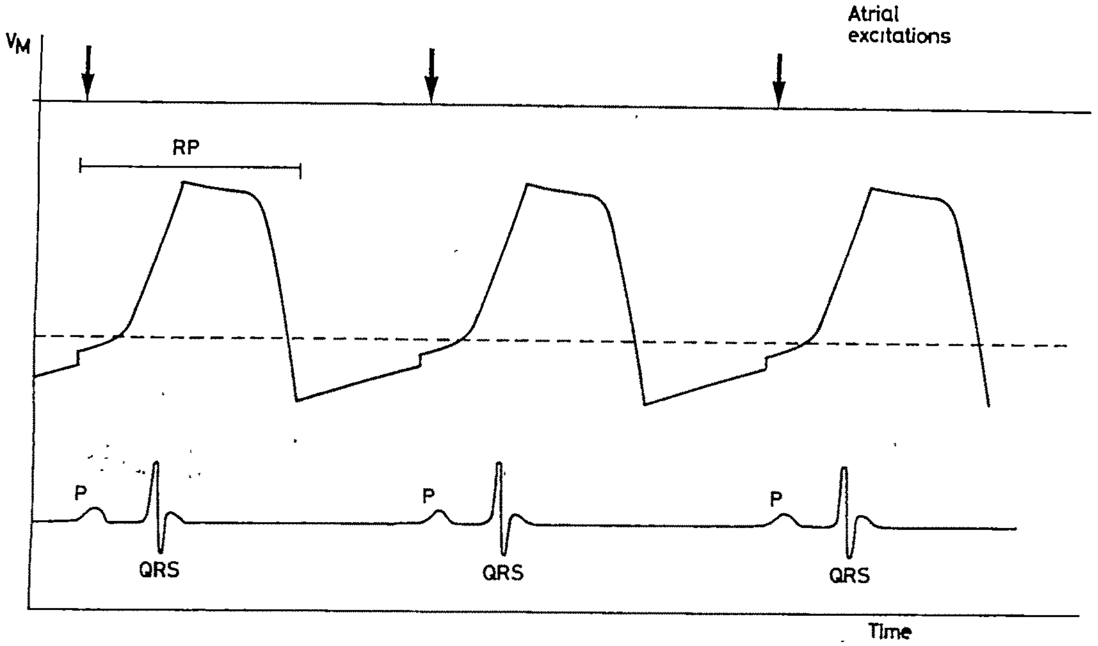


Fig 2 *Hypothetical model of the atrioventricular nodal pacemaker during sinus rhythm. The ventricular rate and PR interval depend on the sinus rate and the slope of phase 4 depolarisation of the atrioventricular nodal pacemaker. During sinus rhythm or any other organised atrial rhythm the electrotonic effect of the atrial excitations is constant. Varying PR intervals during sinus arrhythmias, long PR intervals of atrial extrasystoles or, for instance, concealed conduction of a non-transmitted P wave can be explained by this model.*

would depend on the random electrical properties of the fibrillating atria[42] and the refractoriness and the intrinsic rate of the atrioventricular nodal pacemaker. The rate of the atrioventricular nodal pacemaker in turn could be increased or decreased by the autonomic nervous system.[46 47] Similarly, anterograde block during right ventricular pacing in the presence of atrial fibrillation might be attributed to concealed retrograde conduction of the ventricular depolarisations with overdrive suppression of the atrioventricular nodal pacemaker.[20 48]

Entrainment of the atrioventricular node

If we assume that the atrioventricular node acts as a biological pacemaker or oscillator, then when atrial rhythms are organised atrioventricular "coupling" could result because of synchronisation (entrainment) of the atrioventricular node by the electrotonic spread of the atrial wave of excitation (fig 2).

In 1940 Katz and Schmitt described the electric interaction between two adjacent nerve fibres, which they called "synchronisation".[49] In 1947 Segers *et al* first referred to possible synchronisation of the atrioventricular nodal pacemaker, namely a fixed temporal relation between the atria and ventricles resulting in isorhythmic dissociation.[50] This phenomenon is known as acchrochage, a term which Segers introduced in 1946, when he discovered two fragments of a frog's heart that beat in phase when they were brought into physical contact.[51]

DEFINITION OF ENTRAINMENT

Jalife and Michaels defined entrainment as the coupling of a self sustained oscillatory system (such as a pacemaker) to an external forcing oscillation with the result that either both oscillations have the same frequency or the frequencies are related in a harmonic fashion.[52] Winfree defined entrainment as "The locking of one rhythm to another, with N cycles of the one matching M cycles of the other" and suggested that cardiac pacemaker cells may be synchronised by electrotonic interaction.[53] This ability of most non-linear oscillators to entrain or synchronise rests on their time-dependent sensitivity. A probable cellular electrophysiological mechanism responsible for entrainment and synchronisation is an alteration of the rate of phase 4 depolarisation of pacemaker cells. Van der Tweel *et al* in 1973 showed that a pacemaker does not need to be ectopic to be synchronised or entrained.[55] After the introduction of the concept of entrainment in cardiac electrophysiology by Segers *et al*,[50 51] Moe *et al* systematically investigated the electrophysiological mechanisms of synchronisation and entrainment of cardiac pacemakers.[54-58]

Waldo *et al* introduced the term "transient entrainment" to explain the observation that the rate of a tachycardia can be increased by a more rapid electronic pacing rate.[59] This form of entrainment[60] differs from the original concept in that the pacemaker rate can not only be increased but also decreased. The concept that we believe to be most appropriate, based on available evidence, is that of the entrained biological oscillator as defined by Winfree[53 61] and Jalife and Michaels.[52]

SINUS RHYTHM

Entrainment of the atrioventricular nodal pacemaker during sinus rhythm by an atrial impulse would explain the paradoxically comparatively short PR intervals in hearts of large mammals such as elephants and whales[62-64] which have much larger atrioventricular nodes than those of human beings.[65 66] If during sinus rhythm the atrioventricular node acts as an entrained pacemaker or oscillator, atrioventricular nodal delay need no longer be dependent on the size of the atrioventricular node, or cable length, nor would the short atrioventricular nodal delay in such large hearts conflict with the expected protection against high atrial rates.[28 29] This assumption would be strengthened were the atrioventricular nodal pacemaker located at the NH-H border[67] so that it would promptly activate the His-Purkinje system. The presence of monophasic action potentials with a distinct diastolic depolarisation in the NH-region[11 17] localises the atrioventricular nodal pacemaker to that specific area within the atrioventricular node.

The concept of a biological oscillator also explains the shortening of the PR interval during sinus tachycardia induced by sympathetic stimulation or physical exercise. In contrast with atrial tachycardia or rapid atrial pacing (see below), the sympathetic drive not only affects the frequency of the sinus pacemaker and the atrial rate, but also the intrinsic rate of the atrioventricular nodal pacemaker and thus the rate of rise of phase 4 depolarisation. The steeper phase 4, the earlier is the threshold potential reached and the shorter the PR interval (fig 2).

RETROGRADE (VENTRICULOATRIAL) CONDUCTION

In 1959 Scherf used the concept of electrotonic spread to explain retrograde conduction with a relatively short RP interval in the presence of complete atrioventricular block.[68] Since the strength of the electrotonic spread of the ventricular excitation wave may well exceed that of the atrial excitation wave it seems logical that retrograde (ventriculoatrial) "conduction" may be present during partial or complete anterograde (atrioventricular) block.[69 70] This concept could also explain why structural damage of the atrioventricular junction impairs anterograde conduction more than retrograde conduction. In this setting, however, the geometry of the atrioventricular junction may also be important. If we assume that electrotonic spread can result in retrograde conduction in the presence of atrioventricular block, it is reasonable to expect that it also operates in the absence of atrioventricular block. Similarly, if the electrotonic spread is responsible for retrograde conduction, it may also be the mechanism of anterograde conduction.

Also the findings by Akhtar *et al* that anterograde (atrioventricular) conduction can be affected by retrograde (ventriculoatrial) conduction, and the other way round,[71-73] can be explained by electrotonic spread. For instance, a concealed retrogradely conducted ventricular impulse could cause an early resetting of the atrioventricular nodal pacemaker and thus facilitate anterograde conduction.

ATRIAL TACHYCARDIA

If the atrioventricular nodal pacemaker is electrotonically coupled to the sinus node by atrial excitation what is the effect of atrial tachycardias or rapid atrial pacing on atrioventricular nodal function? Atrial arrhythmias with high rates could be blocked by either an insufficiently strong electrotonic effect on phase 4 depolarisation in the presence of a relatively slow intrinsic rate of the atrioventricular nodal pacemaker or by entrainment in a higher harmonic fashion[35 52] as, for example, during atrial flutter with atrioventricular block. Van der Tweel *et al* have shown that this manifestation of entrainment operates at the level of the sinoatrial node of isolated rat hearts.[35] There is probably an upper limit to which the intrinsic oscillatory rate of the atrioventricular nodal pacemaker can be increased by an artificial pacemaker or an ectopic focus. At that point its rate can no longer be enhanced through entrainment by the artificial atrial pacemaker. Long PR intervals, and, subsequently, Wenckebach periodicity may result when the atrial and the atrioventricular nodal pacemaker rates are out of phase. Wenckebach type I atrioventricular block may also result from damage below the assumed location of the atrioventricular nodal pacemaker, from too low an intrinsic rate of the atrioventricular nodal pacemaker, or from impaired conduction in the His-Purkinje system. In the absence of sympathetic influences the rate of phase 4 depolarisation does not increase and it takes longer to reach threshold. The coupling of the ventricles to the atria occurs at the moment the electrotonic spread of the atrial excitation reaches the atrioventricular nodal pacemaker. An impulse arriving early in diastole or in the presence of a slow phase 4 depolarisation, or both, will result in a long PR interval. On the contrary, an impulse arriving late in diastole or in the presence of a fast phase 4 depolarisation, or both, will result in a short PR interval (fig 2).

ACCESSORY PATHWAYS

In the presence of a Kent bundle or other accessory pathways the concept of the atrioventricular node as an oscillator would change the current notion that competition between two conduction pathways with different electrophysiological properties is the mechanism of Wolff-Parkinson-White syndrome.[74-76] The competition (fusion) would rather be between a passive, at times rapidly conducting pathway and a synchronised, entrained biological oscillator located in the atrioventricular node. Conduction through the accessory pathway that results in ventricular excitation could either cause overdrive suppression of the atrioventricular node and thus force the atrial impulse to procede along the accessory pathway, or it could reset the atrioventricular nodal pacemaker and activate the atrial myocardium, resulting in an atrioventricular reentrant tachycardia.

Conclusion

There can be no doubt about the importance of electrotonus as the mechanism of otherwise inexplicable arrhythmias.[77-80] In this presentation the atrioventricular node is regarded as a biological oscillator and electrotonus induced by organised atrial or ventricular excitation as the mechanism by which the oscillator can be entrained.

The concept of the atrioventricular node as an oscillator/pacemaker influenced by electrotonus is in keeping with the functions of the atrioventricular node and offers a rational explanation for the varying atrioventricular nodal delay during sinus rhythm, the protection the atrioventricular node affords in the presence of atrial tachycardias and fibrillation, and for atrioventricular nodal automaticity as an escape mechanism. The concept accords with clinical and experimental observations that classically have been attributed to the "conducting" properties of the atrioventricular junction. It also offers a rational explanation for the relatively short PR intervals in large mammals such as elephants and whales, as well as for several atrioventricular "conduction" abnormalities and arrhythmias. In fact, the assumption that conduction and automaticity are properties of the atrioventricular node tends to complicate rather than to clarify the understanding of atrioventricular nodal function under varying physiological and pathological influences.

The question whether the atrioventricular node conducts in the traditional meaning of the word warrants further investigation.

This study was supported by the Wijnand M Pon Foundation, Leusden, The Netherlands.

We thank Dr Suzanne B Knoebel for her contribution to the concept and the preparation of this paper.

References

1 Fye WB. The origin of the heart beat: a tale of frogs, jellyfish, and turtles. *Circulation* 1987;76:493–500.
2 Engelmann TW. Beobachtungen und Versuche am suspendierten Herzens. *Pflugers Archiv f d ges Physiol* 1894;56·149–202.
3 Tawara S. *Das Reizleitungssystem des Herzens.* Jena: Fischer, 1906.
4 Aschoff L. Referat uber die Herzstorungen in ihren Beziehungen zu den spezifischen Muskelsystemen des Herzens. *Verh d path Ges* 1910;**14**:3–35.
5 Von Hosslin H. Über Veranderungen der Kammerkomplexe im Elektrokardiogramm bei normaler Vorhofstatigkeit und Vorhofflimmern. *Zeitschr f d ges exp Med* 1923;34:358–72.
6 Mobitz W. Über die unvollständige Störung der Erregungsuberleitung zwischen Vorhof und Kammer des menschlichen Herzens. *Zeitschr f d ges exp Med* 1924;4:180–237.
7 Donzelot E. La dualité normale de l'automatisme cardiaque. *Arch Mal Coeur* 1924;17:409–14.
8 Vaquez H, Donzelot E. Physiologie du rythme cardiaque. *Arch Mal Coeur* 1925;**18**:353–70.
9 Gilson AS Jr The locus and the nature of the A-V pause in the spread of cardiac activation. *Am J Physiol* 1942;**138**:113–25.
10 Scherf D, Cohen J. *The atrioventricular node and selected cardiac arrhythmias.* New York: Grune and Stratton, 1964:23–32.
11 Hoffman BF, Paes de Carvalho A, de Mello WC. Transmembrane potentials of single fibres of the atrioventricular node. *Nature* 1958;**181**:66–7.
12 Hoffman BF, Cranefield PF. Microelectrode studies of possible mechanisms of atrioventricular delay. *Physiologist* 1959,2:59–60.
13 Scher AM, Rodriguez MI, Liikane J, Young AC. The mechanism of atrioventricular conduction. *Circ Res* 1959;7:54–61.
14 Van der Kooi MW, Durrer D, Van Dam RTh, Van der Tweel LH. Electrical activity in sinus node and atrioventricular node. *Am Heart J* 1956;**51**:684–700.
15 Hoffman BF, Cranefield PF. *Electrophysiology of the heart.* New York: McGraw-Hill, 1960:23 ff.
16 Janse MJ. Influence of the direction of the atrial wave front on A-V nodal transmission in isolated hearts of rabbits *Circ Res* 1969;**25**:439–49.
17 Mazgalev T, Dreifus LS, Iinuma H, Michelson EL.

Effects of the site and timing of atrioventricular nodal input on atrioventricular conduction in the isolated perfused rabbit heart. *Circulation* 1984;**70**:748–59.

18 Durrer D, Van der Tweel LH. Excitation of the left ventricular wall of the dog and goat. *Ann NY Acad Sci* 1957;**65**:779–803.

19 Durrer D, Van Dam RTh, Freud GE, Janse MJ, Meijler FL, Arzbaecher RC. Total excitation of the isolated human heart. *Circulation* 1970;**41**:899–912.

20 Wittkampf FHM, De Jongste MJL, Lie KI, Meijler FL. Effect of right ventricular pacing on ventricular rhythm during atrial fibrillation. *J Am Coll Cardiol* 1988;**11**:539–45.

21 Grant RP. The mechanism of A-V arrhythmias with an electronic analogue of the human A-V node. *Am J Med* 1956;**20**:334–44.

22 Lewis T. *The mechanism and graphic registration of the heart beat*. London: Shaw and Sons, 1925:377.

23 Mackenzie J. The nature and significance of heart symptoms: II. The reflex process and the heart beat. *Br Med J* 1922;**1**:551–3.

24 Mobitz W. Zur Frage der atrioventrikularen Automatie. *D Arch f klin Med* 1923;**141**:257–89.

25 Dagget WM, Bianco JA, Powell WJ, Austen WG. Relative contributions of the atrial systole-ventricular systole interval and of patterns of ventricular activation to ventricular function during electrical pacing of the dog heart. *Circ Res* 1970;**27**:69–79.

26 Clark AJ. Conduction in the heart of mammals In: *Comparative physiology of the heart*. Cambridge: Cambridge University Press, 1927.49–51.

27 Altman PL, Dittmer DS. *Biological handbooks: respiration and circulation*. Bethesda, Maryland: FASEB, 1971:278.

28 Boineau JP, Moore EN. Evidence for propagation of activation across an accessory atrioventricular connection in types A and B pre-excitation. *Circulation* 1970;**41**:375–97.

29 Dreifus LS, Haiat R, Watanabe Y, Arriaga J, Reitman N. Ventricular fibrillation. A possible mechanism of sudden death in patients with Wolff-Parkinson-White syndrome. *Circulation* 1971;**43**:520-7.

30 Wenckebach KF, Winterberg H. *Die Unregelmassige Herztätigkeit*. Leipzig: Wilhelm Engelmann, 1927:325–7.

31 Van der Pol B, Van der Mark J. The heart beat considered as a relaxation oscillation and an electrical model of the heart. *Arch Neerl Physiol* 1929;**14**: 418–43.

32 Bethe A. Die biologische Rhythmus-Phanomene als selbstandige bzw. erzwungene Kippvorgange betrachtet. *Pflugers Arch f d ges Physiol* 1940;**244**.1–42.

33 Van der Tweel LH, Meijler FL, Van Capelle FJL. Synchronization of the heart. *J Appl Physiol* 1973; **34**:283–7.

34 Urthaler F, Katholi CR, Macy J, James TN. Mathematical relationship between automaticity of the sinus node and the AV junction. *Am Heart J* 1973;**86**:189–95.

35 Katholi CR, Urthaler F, Macy J, James TN. A mathematical model of automaticity in the sinus node and AV junction based on weakly coupled relaxation oscillations. *Comp Biomed Res* 1977;**10**.529–43.

36 West BJ, Goldberger AL, Rovner G, Bhargava V Nonlinear dynamics of the heart beat. The AV function passive conduit or active oscillator? *Physica* 1985;**17D**:198–206.

37 Schamroth L, Martin DH, Pachter M. The extrasystolic mechanism as the entrainment of an oscillator. *Am Heart J* 1988;**115**:1363–8.

38 Cohen RJ, Berger RD, Dushane TE. Quantitative model for the ventricular response during atrial fibrillation. *IEEE Trans Biomed Eng* 1983;**30**:769–80.

39 Van der Tweel I, Herbschleb JN, Borst C, Meijler FL. Deterministic model of the canine atrioventricular node as a periodically perturbed, biological oscillator. *J Appl Cardiol* 1986;**1**:157–73.

40 Brody DA. Ventricular rate patterns in atrial fibrillation. *Circulation* 1970;**41**:733–5.

41 Bootsma BK, Hoelen AJ, Strackee J, Meijler FL. Analysis of RR intervals in patients with atrial fibrillation at rest and during exercise. *Circulation* 1970;**41**:783–94

42 Kirsh JA, Sahakian AV, Baerman JM, Swiryn S. Ventricular response to atrial fibrillation· Role of atrioventricular conduction pathways. *J Am Coll Cardiol* 1988;**12**:1265–72.

43 Langendorf R, Pick A, Katz LN. Ventricular response in atrial fibrillation· role of concealed conduction in the AV junction. *Circulation* 1965;**32**:69–75

44 Moore EN. Observations on concealed conduction in atrial fibrillation. *Circ Res* 1967;**21**:201–8.

45 Dreifus LS, Mazgalev T. "Atrial paralysis": does it explain the irregular ventricular rate during atrial fibrillation? *J Am Coll Cardiol* 1988;**11**:546–7.

46 Borst C, Meijler FL. Baroreflex modulation of ventricular rhythm in atrial fibrillation. *Eur Heart J* 1984;**5**:870–5

47 Meijler FL, Kroneman J, Van der Tweel I, Herbschleb JN, Heethaar RM, Borst C. Nonrandom ventricular rhythm in horses with atrial fibrillation and its significance for patients. *J Am Coll Cardiol* 1984; **4**:316–23.

48 De Jongste MJL, Wittkampf FHM, Lie KI, Van der Tweel I, Meijler FL. Regularization of ventricular rhythm by right ventricular pacing in patients with atrial fibrillation [Abstract]. *Circulation* 1985; **72**(suppl III):32.

49 Katz B, Schmitt O. Electric interaction between two adjacent nerve fibres *J Physiol* 1940;**97**:471–88.

50 Segers M, Lequime J, Denolin H. Synchronization of auricular and ventricular beats during complete heart block. *Am Heart J* 1947;**33**:685–91.

51 Segers M. Les phénomènes de synchronisation au niveau du coeur. *Arch Int Physiol* 1946;**54**:87–106.

52 Jalife J, Michaels DC. Phase-dependent interactions of cardiac pacemakers on mechanisms of control and synchronization in the heart. In: Zipes DP, Jalife J, eds. *Cardiac electrophysiology and cardiac arrhythmias*. New York: Grune and Stratton, 1985:109–19.

53 Winfree AT. *When time breaks down. The three dimensional dynamics of electrochemical waves and cardiac arrhythmias*. Princeton, New Jersey: Princeton University Press, 1987.

54 Jalife J, Moe GK. Effect of electrotonic potentials on pacemaker activity in canine Purkinje fibers in relation to parasystole. *Circ Res* 1976;**39**:801–8.

55 Jalife J, Moe GK. A biological model of parasystole. *Am J Cardiol* 1979,**43**:761–72.

56 Delmar M, Jalife J, Michaels DC. Effects of changes in excitability and intracellular coupling on synchronization in the rabbit sino-atrial node. *J Physiol* 1986;**370**:127–50.

57 Michaels DC, Matyas EP, Jalife J. Dynamic interactions and mutual synchronization of sinoatrial node pacemaker cells. *Circ Res* 1986;**58**:706–20.

58 Antzelevitch C, Jalife J, Moe GK. Electrotonic modulation of pacemaker activity. Further biological and mathematical observations on the behaviour of modulated parasystole. *Circulation* 1982;**66**:1225–32.

59 Waldo AL, Henthorn RW, Plump VJ, MacLean WAH. Demonstration of the mechanism of transient entrainment and interruption of ventricular tachycardia with rapid atrial pacing. *J Am Coll Cardiol* 1984;**3**.422–30.

60 Brugada P, Wellens HJJ. Entrainment as an electrophysiologic phenomenon. *J Am Coll Cardiol* 1984; **3**:451–4.

61 Winfree AT. Biological rhythms and the behavior of populations of coupled oscillators. *J Theor Biol* 1967;**16**:15–42.

62 Meijler FL. Atrioventricular conduction versus heart size from mouse to whale. *J Am Coll Cardiol* 1985; **5**:363–5.

63 Meijler FL. Comparative aspects of the dual role of the human atrioventricular node. *Br Heart J* 1986; **55**:286–90.

64 Meijler FL, Janse MJ. Morphology and electrophysiology of the mammalian atrioventricular node. *Physiol Rev* 1988;**68**:608–47.

65 Truex RC, Smythe MQ. Comparative morphology of the cardiac conduction tissue in animals. *Ann NY Acad Sci* 1965;**127**:19–33.

66 White PD, Kerr W. The heart of the sperm whale with special reference to the A-V conduction system. *Heart* 1915/1917;**6**:207–10.

67 James TN. Structure and function of the AV junction. *Jpn Circ J* 1983;**47**:1–47.

68 Scherf D. Retrograde conduction in complete heart block. *Dis Chest* 1959;**35**:320–1.

69 Winternitz M, Langendorf R. Auriculo-ventricular block with ventriculo-auricular response: report of six cases and critical review of the literature. *Am Heart J* 1944;**27**:301–21.

70 Schuilenberg RM. Patterns of V-A conduction in the human heart in the presence of normal and abnormal A-V conduction. In: Wellens HJJ, Lie KI, Janse MJ, eds. *The conduction system of the heart.* Leiden: Stenfert Kroese, 1976. 485–504.

71 Akhtar M, Damato AN, Batsford WP, Ruskin JN, Ogunkelu JB. A comparative analysis of antegrade and retrograde conduction patterns in man. *Circulation* 1975;**52**:766–78.

72 Shenasa M, Denker S, Mahmud R, Lehmann M, Gilbert CJ, Akhtar M. Atrioventricular nodal conduction and refractoriness after intranodal collision from antegrade and retrograde impulses. *Circulation* 1983;**67**:651–60.

73 Lehmann MH, Rehan M, Denkar S, Soni J, Akhtar M. Retrograde concealed conduction in the atrioventricular node: differential manifestations related to level of intranodal penetration. *Circulation* 1984; **70**:392–401.

74 Meijler FL. Latent pre-excitation: exposure of anterograde accessory pathway conduction during atrial fibrillation [Letter]. *Br Heart J* 1988;**60**:93–4

75 Krikler DM, Rowland E. Concealed pre-excitation. *J Electrocardiol* 1978;**11**:209–11.

76 Milstein S, Klein SL, Rattes MF, Sharma AD, Yee R. Comparison of the ventricular response during atrial fibrillation in patients with enhanced atrioventricular node conduction and Wolff-Parkinson-White syndrome. *J Am Coll Cardiol* 1987;**10**:1244–8

77 Fisch C, Knoebel SB. "Wedensky facilitation" in the human heart. *Am Heart J* 1968;**76**:90–2.

78 Scherf D, Schott A. *Extrasystoles and allied arrhythmias.* Chicago: William Heinemann, 1973: 252–4.

79 Oreto G, Satullo G, Luzza F, Schamroth L. Electrotonic inhibition of an idioventricular escape focus by nonconducted sinus impulses. *Am Heart J* 1988,**116**:1097–9.

80 Saoudi N, Castellanos A, Galtier M, *et al.* Unusual electrocardiographic patterns of modulated parasystole. *Eur Heart J* 1987;**8**:1229–35.

Br Heart J 1989;61:316–21

A double blind placebo controlled study of early and late administration of recombinant tissue plasminogen activator in acute myocardial infarction

A J McNEILL, S R CUNNINGHAM, D J FLANNERY, G W N DALZELL, C M WILSON, N P S CAMPBELL, M M KHAN, G C PATTERSON, S W WEBB, A A J ADGEY

From the Regional Medical Cardiology Centre, Royal Victoria Hospital, Belfast, Northern Ireland

SUMMARY Within four hours of the onset of acute myocardial infarction 57 consecutive patients were randomised blindly to infusion of 150 mg recombinant tissue plasminogen activator (rt-PA) (group 1) over five hours or placebo (group 2) when they were first seen outside hospital or in the accident and emergency department. When they were admitted to the coronary care unit patients in group 1 also had placebo infused and those in group 2 were treated with rt-PA as well as placebo. Treatment with rt-PA started at a mean of 119 minutes (range 38–235) after the onset of pain in group 1 and 187 minutes (range 80–285) after the onset of pain in group 2. In 19 (79%) of 24 in group 1 and 16 of 25 (64%) in group 2 cardiac catheterisation 10–14 days after infarction showed thrombolysis in myocardial infarction grades 2 or 3. There was a mean percentage shortening of the infarct related segments (Leighton method) of 16% in group 1 and 10·3% in group 2. For patients with anterior infarction mean percentage shortening was 20·5% in group 1 and 12·2% in group 2. Although there was no significant difference in global ejection fraction as assessed by contrast ventriculography or radionuclide ventriculography the infarct related regional third ejection fraction (a measure of the function of the territory of the affected coronary artery) was significantly improved by early treatment (41% group 1 and 28% group 2). Assessment of infarct size by the QRS scoring method of Palmeri showed QRS score ≤3 in 15/25 patients in group 1 and 8/27 in group 2. Nine patients developed 11 episodes of ventricular fibrillation; all patients in whom ventricular fibrillation developed during treatment with rt-PA were successfully resuscitated. There was no clinically significant bleeding. In seven (12%) patients clinical and electrocardiographic criteria suggested reocclusion. Five patients died from cardiac causes.

Prehospital administration of rt-PA was feasible and significantly reduced the delay before thrombolysis was started. Earlier treatment improved myocardial function in the infarct area and reduced the infarct size.

Recombinant tissue plasminogen activator (rt-PA) used in the acute phase of myocardial infarction is an effective thrombolytic agent that improves left ventricular function after clot lysis.[1,2] In dogs the metabolic changes induced by ischaemia increased with time from the onset of experimental occlusion of a coronary artery.[3] It follows that earlier lysis of an occluding thrombus in the coronary artery of a patient with evolving acute myocardial infarction should further limit myocardial damage and reduce infarct size, and thus improve left ventricular function. To test this hypothesis we performed a double blind placebo controlled study to compare early and late administration of rt-PA to patients in whom treatment started within four hours of the onset of acute myocardial infarction.

Patients and methods

Patients with suspected acute myocardial infarction seen outside hospital by staff on the mobile coronary care unit or in the accident and emergency depart-

Requests for reprints to Dr A A J Adgey, Regional Medical Cardiology Centre, Royal Victoria Hospital, Belfast BT12 6BA, Northern Ireland.

Accepted for publication 10 November 1988

ment of the hospital were considered for entry into the study. All were aged less than 75 years, had had chest pain lasting less than four hours, and had ST segment elevation of 1 mm in at least two standard leads or in two precordial leads of the electrocardiogram. We excluded women of childbearing age; patients with previous cerebrovascular stroke, a history of generalised bleeding diathesis, or recent trauma or operation; or left bundle branch block on the electrocardiogram.

Continuous electrocardiographic monitoring was started, an intravenous cannula was put in place, and diamorphine was given for pain relief. rt-PA (double chain) and placebo for each patient were supplied by Wellcome research laboratories in pre-packed cartons that were used in sequence. When patients became pain free they were randomised blindly to receive rt-PA (group 1) or placebo (group 2). Allocation depended on whether the first colour coded section of the carton contained placebo or active agent. The contents of the vials from this section were dissolved and infused intravenously (fig 1). Patients then proceeded directly to the coronary care unit where the contents from the second section of the same carton were dissolved and infused, via a line in the contralateral arm, concurrently and at the same rate as the first infusion. Thus patients in group 1 started treatment with rt-PA before admission to the coronary care unit whereas those in group 2 started rt-PA after admission to the coronary care unit. rt-PA (100 or 115 mg) was infused intravenously over 90 minutes and 50 or 35 mg respectively was infused over the next three and a half hours. Intravenous heparin (1000 units/h) was started at the end of the first infusion. Battery powered infusion pumps (Graseby MS 2000 and Graseby MS 16A) were used to deliver rt-PA, placebo, and heparin at the desired rate.

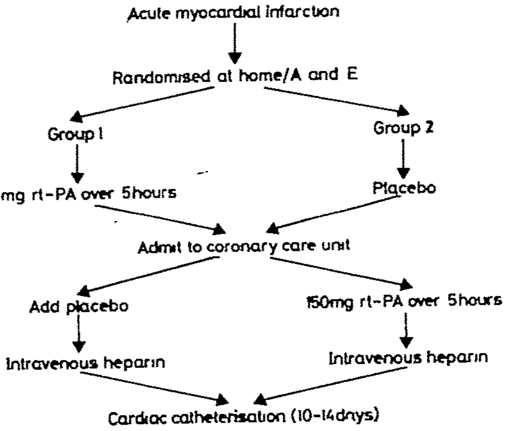


Fig 1 *Plan of the study.*

Patients had standard coronary care including continuous electrocardiographic monitoring before and during admission to the coronary care unit. Throughout their hospital stay, bleeding and other complications were noted.

Infarct size was assessed by the QRS scoring method of Palmeri *et al.*[4] Electrocardiograms recorded 48–72 hours after infarction were assessed by an investigator who was unaware of the treatment group. Cardiac catheterisation was performed by the Judkins technique at 10–14 days after infarction or earlier if clinically indicated. Contrast ventriculography was performed in the right anterior oblique 30° view and selective coronary angiography was carried out. The global ejection fraction was calculated according to Dodge's area/length method, and regional wall movement in the infarct area was assessed by Leighton's method.[5] Segments 2 and 3 were used to assess anterior infarction and 7 and 8 for inferior infarction (figs 2–4). Coronary angiograms were scored by the thrombolysis in myocardial infarction (TIMI) grades (0–3).[6] All angiograms and ventriculograms were assessed by experienced investigators who were unaware of the treatment group. Gated blood pool scanning was performed whenever possible during hospital admission or soon after discharge. Global ejection fraction and infarct related regional third ejection fraction (used as a measure of function in the area of infarction) were calculated by an investigator who was unaware of the patient's treatment group. Gated blood pool scanning was performed with an Ohio-Nuclear Sigma 420 Gamma Camera interfaced to an MCS-560 Nuclear Medicine Computer for acquisition and processing data. Global ejection fraction was

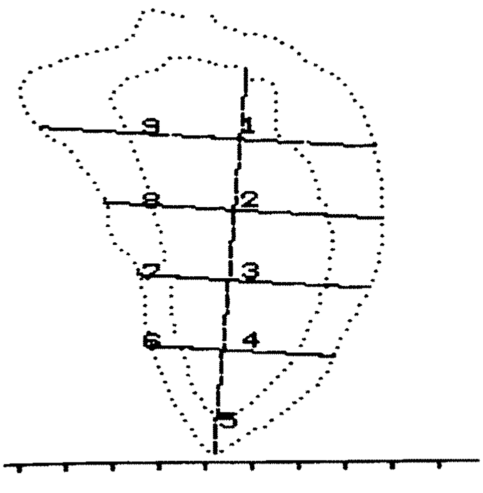


Fig 2 *Computer printout of a normal left ventriculogram assessed by the Leighton method.*

measured in the standard way. After calculation of global ejection fraction the infarct related regional third ejection fraction was calculated for each of the thirds of the ventricle subtended by the three main coronary arteries. Thus the inferoapical ,ejection fraction was used as a measure of function of the territory of the right coronary artery, the anteroseptal for the left anterior descending, and posterolateral for the circumflex coronary artery. Infarct related regional third ejection fraction was calculated by standard software incorporated in the system. The program defined the centre of the left ventricular image in diastole and then defined three sectors of 120° that correspond to the area of the left ventricle subtended by each of the three coronary arteries.

Univariate methods of analysis are used throughout the paper. For assessment of time to onset of treatment, global and infarct related regional third ejection fraction, and regional wall movement we used Student's *t* test for unpaired data. QRS scores were assessed by the χ^2 test.

We obtained the approval of the research ethical committee of the Faculty of Medicine, Queen's University of Belfast before we started the study.

Results

Fifty-seven consecutive patients (47 men, 10 women) mean age 58 years (37–74 years) were studied. Forty nine patients were first seen by staff in the mobile coronary care unit and eight were seen in the accident and emergency department. Twenty seven patients entered group 1 and 30 group 2. There was no significant difference in infarct distribution or previous history of infarction (table 1). Infusion of rt-PA was started a mean of 119 minutes (range 38–235) after the onset of pain in group 1 and after a mean of 187 minutes in group 2 (range 80–285) (p = 0·0005, 95% confidence interval 35 to 101) (table 2).

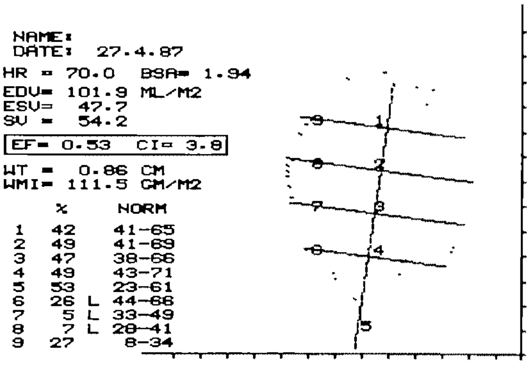

```
NAME:
DATE:  27.4.87
HR = 70.0  BSA= 1.94
EDV= 101.9 ML/M2
ESV=  47.7
SV =  54.2
EF= 0.53  CI= 3.8
WT =  0.86 CM
WMI= 111.5 GM/M2
      %      NORM
1    42      41-65
2    49      41-69
3    47      38-66
4    49      43-71
5    53      23-61
6    26  L   44-66
7     5  L   33-49
8     7  L   28-41
9    27       8-34
```

Fig 3 *Leighton assessment of a ventriculogram from a patient with inferior infarction. Hypokinesis was greatest in segments 7 and 8. HR, heart rate; BSA, body surface area; EDV, end diastolic volume; ESV, end systolic volume; SV, stroke volume; EF, ejection fraction; CI, cardiac index; WT, wall thickness; WMI, wall mass index; L, hypokinetic segment.*

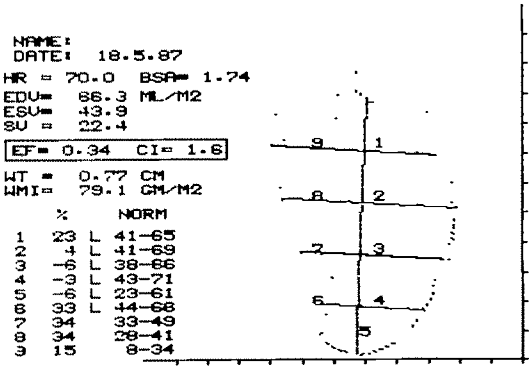

```
NAME:
DATE:  18.5.87
HR = 70.0  BSA= 1.74
EDV=  66.3 ML/M2
ESV=  43.9
SV =  22.4
EF= 0.34  CI= 1.6
WT =  0.77 CM
WMI=  79.1 GM/M2
      %      NORM
1    23  L   41-65
2     4  L   41-69
3    -6  L   38-66
4    -3  L   43-71
5    -6  L   23-61
6    33  L   44-68
7    34      33-49
8    34      28-41
3    15       8-34
```

Fig 4 *Leighton assessment of a ventriculogram from a patient with anterior infarction. See legend to fig 3 for abbreviations.*

Reperfusion was assessed from coronary angiograms performed a mean of 10·7 days after infarction in group 1 and 11·5 days after infarction in group 2. TIMI grade 2 or 3 thrombolysis was seen in 19/24 (79%) of assessable coronary angiograms in group 1 and 16/25 (64%) in group 2. Five patients died before angiography, one patient had a reinfarction and was given a second dose of rt-PA before angiography, and in two patients disease was so severe in all three vessels that the infarct related artery could not be identified with certainty.

There was no difference in mean global ejection fraction between the two groups (table 3). Table 4 shows the percentage shortening of the infarct related segments as assessed by the Leighton method. The difference in mean percentage shortening between the two groups is just outside the conventional 95% level of significance (16% *v* 10·3%, p = 0·06, 95% confidence interval −1·6 to 13). However, for patients with anterior myocardial infarction the mean (SEM) percentage shortening was significantly bet-

Table 1 *Infarct distribution and previous history of myocardial infarction (MI)*

	Group 1 *27 patients*	*Group 2* *30 patients*
Infarct:		
Anterior	13	18
Inferior	14	11
Lateral	0	1
Previous MI:		
0	22	24
1	3	5
2	1	0
>2	1	1

Table 2 *Time to start of first and second infusion for groups 1 and 2*

	Mean time to 1st infusion (min)	*Mean time to 2nd infusion (min)*
Group 1	rt-PA 119*	Placebo 169
Group 2	Placebo 129	rt-PA 187*

*p = 0·0005

ter for those treated early (20·5 (2·99)%) than for those treated late (12·2 (2·23)%) ($p = 0·01$, 95% confidence interval 0·9 to 15·7).

There was no significant difference between the two groups when the global ejection fraction was assessed by radionuclide ventriculography (table 5). However, the infarct related regional third ejection fraction was significantly better for patients in group 1 (41%) than in group 2 (28%) ($p < 0·05$, 95% confidence interval −0·8 to 26·8) (one tailed *t* test).

The QRS scoring method of Palmeri *et al* showed that 15/25 patients from group 1 had a QRS score ≤3 compared with 8/27 from group 2 ($\chi^2 = 4·84$, $p < 0·05$). Of the remaining five patients one had Wolff-Parkinson-White syndrome, one right bundle branch block, and three died before the 48–72 hour electrocardiogram was performed.

Nine patients developed 11 episodes of ventricular fibrillation—four patients from group 1 and five from group 2. Of the 11 episodes, seven occurred during treatment with rt-PA, one occurred during placebo, and three occurred after rt-PA infusion (one on day 2 and one on day 5 after infarction and one on day 7 during reinfarction). There were three episodes of ventricular fibrillation during treatment with rt-PA before admission to the coronary care unit and in all three cases resuscitation was successful. Seven of the nine patients with ventricular fibrillation were initially resuscitated and six survived to leave hospital.

In 27 patients there was minor cutaneous bruising at sites of venepuncture or catheterisation or both. One patient developed a bloody ooze from a recent tooth extraction site, one had coffee ground vomit, and two had haematuria (soon after bladder catheterisation in one). No patient required transfusion.

In seven (12%) patients (three in group 1 and four in group 2) clinical and electrocardiographic criteria suggested reocclusion. One of these received a second dose of rt-PA with successful reperfusion.

Table 3 *Left ventricular angiography.*

	Mean global ejection fraction (%)	
	Group 1	*Group 2*
All infarcts	50	48
Anterior	49 (n = 13)	44 (n = 15)
Inferior	51 (n = 11)	55 (n = 11)

Table 4 *Mean (SEM) percentage shortening of the infarct related segments as assessed by the Leighton method*

	Treatment group				
Infarct site	*Group 1*		*Group 2*		*p*
All sites	16·0	(2·72)	10·3	(2·56)	0·06
Anterior	20·5	(2·99)	12·2	(2·23)	0·01
Inferior	10·7	(4·58)	7·7	(5·26)	0·34

Five patients died from cardiac causes: three from cardiogenic shock, one from mesenteric embolisation complicating left ventricular mural thrombus and cardiogenic shock, and one from asystole after ventricular fibrillation. Two of the deaths were in group 1 and three were in group 2.

Discussion

Myocardial damage spreads as a wave front from endocardium to epicardium after occlusion of the infarct related coronary artery. Reducing the delay before lysis of the occluding thrombus is attempted should improve myocardial salvage. Studies of dogs by positron tomography support the hypothesis that earlier removal of the intracoronary thrombus results in greater improvement of myocardial metabolism.[7]

The potential clinical benefit of early thrombolytic treatment was evident in the results of the Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico which showed that those treated with streptokinase within the first hour of the onset of symptoms had the greatest reduction in mortality[8] and in the experience with early administration of streptokinase in Jerusalem where patients treated within one and a half hours after the onset of pain had a significantly higher ejection fraction than those treated between one and a half and four hours after the onset of pain.[9] However, neither of these studies was a controlled comparison of early and late treatment—that is the patient population treated early and those treated later may not have been comparable in terms of other treatments, for example time to

Table 5 *Mean global and infarct related regional third ejection fractions as assessed by radionuclide ventriculography*

	Group 1	*Group 2*
Mean time of scan (days)	12·5	12·0
GEF (all grades) (%)	41 (n = 16)	35 (n = 13)
IR RTEF (all grades) (%)	41	28*
IR RTEF (2 and 3 reperfusion) (%)	42	32
IR RTEF (0 and 1 reperfusion) (%)	26	24

*p < 0·05.
GEF, global ejection fraction; IR RTEF, infarct related regional third ejection fraction.

administration of analgesia or oxygen, or to treatment of arrhythmias, or cardiac failure.

In this placebo controlled study we have shown that it is feasible to start thrombolytic treatment with rt-PA outside hospital or in the accident and emergency department. The procedure is safe and significantly reduces the delay in starting thrombolytic treatment. A mean of 68 minutes was saved when rt-PA treatment was started once the diagnosis of myocardial infarction was suspected rather than when the patient was admitted to the coronary care unit. The patient's delay in seeking help caused the greatest delay; transit of the mobile coronary care unit team and the diagnosis of acute infarction and pain relief after arrival of the team with the patient caused less delay.

There were no complications attributable to thrombolytic treatment before admission to hospital. All seven (12%) patients who developed ventricular fibrillation during rt-PA treatment were successfully resuscitated. Ventricular fibrillation was no more common during rt-PA treatment than in an earlier study of acute myocardial infarction without thrombolysis.[10] Concern about arrhythmias during thrombolysis should not preclude rt-PA treatment before admission to hospital provided basic monitoring and resuscitation equipment are available. In most patients reperfusion is usually gradual and therefore less likely to be associated with ventricular fibrillation. Only three episodes of ventricular fibrillation occurred after the initial infusion, one on day 2, one on day 5, and one on day 7 during reinfarction.

Although the trend was towards higher reperfusion rates in those treated early (79% *v* 64%) the difference was not significant. We have already shown that reperfusion rates were improved when rt-PA treatment was started early.[1] It may be that the difference of 68 minutes to the start of rt-PA infusion between these two groups of patients did not significantly affect the reperfusion rate in group 2. rt-PA infusion was started 187 minutes after infarction in group 2 and we know that the angiographically proven reperfusion rate was 82% in patients treated with 100 mg of rt-PA over 90 minutes who were seen within four hours of the onset of acute myocardial infarction.[1] The assessment of reperfusion by angiography at 10–14 days is less accurate than immediate angiography because silent reocclusion or spontaneous reperfusion can occur in the interim. Our patients were catheterised at 10–14 days to allow left ventricular function to be assessed by contrast ventriculography.

Early treatment did not significantly improve mean global left ventricular ejection fraction (tables 3 and 5). However, the infarct related regional third ejection fraction was significantly better in group 1 than in group 2 (41% *v* 28%, $p < 0{\cdot}05$) (table 5) and the improvement in infarct related regional wall movement was almost statistically significant (16·0 (2·7)% *v* 10·3 (2·56)%) ($p = 0{\cdot}06$) (table 4).

In group 1 there were 13 patients with anterior infarction and 14 with inferior infarction and in group 2, 18 patients with anterior infarction, 11 with inferior infarction, and one with lateral infarction. In patients with anterior infarction the regional wall movement was significantly improved by early treatment (20·5 (2·99)% *v* 12·2 (2·23)% ($p = 0{\cdot}01$)). Global ejection fraction is a crude estimate of left ventricular function in patients with infarction because it may be reduced by previous infarction, because hyperkinesis in a non-infarct zone may compensate for hypokinesis in the infarct area, and because return towards normal of this compensatory hyperkinesis may mask thrombolytically induced improvement in the infarct area. This may account for the improvement in left ventricular function in the infarct area without apparent significant improvement in the overall left ventricular ejection fraction as shown by both radionuclide and contrast ventriculography. Left ventricular ejection fraction and regional wall movement were no better in patients with inferior infarction who were treated earlier; nevertheless we believe that thrombolysis should be started as early as possible in patients with inferior infarction because a patent circumflex or right coronary artery may be an important source of collaterals to the anterior surface of the myocardium in patients with previous or future anterior infarction.

The improvement in infarct size with earlier treatment and as assessed by QRS scoring accorded with previous studies of early thrombolytic treatment.[9] Although QRS scoring is a crude estimate of infarct size it correlates well with left ventricular function[4] and is an easily applicable measure of myocardial salvage.

We have shown that thrombolytic treatment can be started safely by medical staff on a mobile coronary care unit; but this is not the only approach to thrombolytic treatment before admission to hospital. In areas where there are no mobile coronary care units with medical staff thrombolysis could be given by general practitioners or suitably trained paramedical personnel with adequate medical supervision probably by telephone. Infusion of rt-PA before hospital admission appreciably reduced the delay in starting thrombolysis. Earlier treatment improved myocardial function in the infarct related area and reduced infarct size. Our results confirm the advantages of reducing the delay before thrombolytic treatment.

We thank the medical, nursing, and paramedical staff of the Regional Medical Cardiology Centre, Royal Victoria Hospital, Belfast, without whose help this work would have been impossible; and Wellcome Research Laboratories for the supply of recombinant tissue plasminogen activator (double chain) and placebo. AJ McN, SRC, and DJF are all Royal Victoria Hospital research fellows.

References

1 McNeill AJ, Shannon JS, Cunningham SR, *et al.* A randomised dose ranging study of recombinant tissue plasminogen activator in acute myocardial infarction. *Br Med J* 1988;**296**:1768–71.

2 National Heart Foundation of Australia Coronary Thrombolysis Group. Coronary thrombolysis and myocardial salvage by tissue plasminogen activator given up to 4 hours after the onset of myocardial infarction. *Lancet* 1988;**i**:203–8.

3 Lie JT, Pairolero PC, Holley KE, McCall JT, Thompson HK Jr, Titus JL. Time course and zonal variations of ischaemia-induced myocardial cationic electrolyte derangements. *Circulation* 1975;**51**:860–6.

4 Palmeri ST, Harrison DG, Cobb FR, *et al.* A QRS scoring system for assessing left ventricular function after myocardial infarction. *N Engl J Med* 1982; **306**:4–9.

5 Leighton RF, Wilt SM, Lewis RP. Detection of hypokinesis by a quantitative analysis of left ventricular cineangiograms. *Circulation* 1974;**50**:121–7.

6 The TIMI study group. The thrombolysis in myocardial infarction (TIMI) trial. Phase 1 findings *N Engl J Med* 1985;**312**:932–6.

7 Bergmann SR, Lerch RA, Fox KAA, *et al.* Temporal dependence of beneficial effects of coronary thrombolysis characterized by positron tomography. *Am J Med* 1982;**73**:573–81.

8 GISSI Study Group. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;**i**·397–401.

9 Koren G, Weiss AT, Hasin Y, *et al.* Prevention of myocardial damage in acute myocardial ischaemia by early treatment with intravenous streptokinase. *N Engl J Med* 1985;**313**:1384–9.

10 Pantridge JF, Webb SW, Adgey AAJ, Geddes JS. The first hour after the onset of acute myocardial infarction. In: Yu PN, Goodwin JF, eds. *Progress in cardiology vol III.* Philadelphia: Lea and Febiger, 1974:173.

Br Heart J 1989;61:322-5

Impact of a policy of direct admission to a coronary care unit on use of thrombolytic treatment

J M A BURNS,* K J HOGG,† A P RAE,* W S HILLIS,† F G DUNN*

*From the Departments of *Cardiology and †Materia Medica, Stobhill General Hospital, Glasgow*

SUMMARY Because thrombolytic treatment is effective only if it is given within six hours of acute myocardial infarction it is vital to admit patients to the coronary care unit as soon as possible after the acute event. A policy of admitting patients directly to the coronary care unit at the request of the patient's general practitioner by a telephone line that is independent of the hospital switchboard significantly reduced the delay. Those admitted via the accident and emergency department at the same hospital reached the coronary care unit 1 h 32 min after the onset of chest pain whereas the 100 patients admitted directly took only 43 minutes. The policy of direct admission also significantly increased both the percentage of patients who received thrombolytic treatment and the percentage of patients admitted within three hours from the onset of symptoms.

The value of thrombolytic treatment in acute myocardial infarction is well established.[1 2] The improvement in left ventricular function and the reduction in mortality were greatest with early thrombolytic treatment.[1-3] Thrombolysis should be attempted as soon as possible after infarction.[4]

We assessed a method for reducing delay in admission to the coronary care unit and what effect this might have on the number of patients suitable for thrombolytic treatment.

Patients and methods

Since 1976 there has been a policy of direct admission to the coronary care unit at Stobhill Hospital, but the extent to which it has been used varied. We discussed this at a clinical meeting with local general practitioners, and identified several difficulties including delay in contacting medical staff via the hospital switchboard at busy times, and the preference of the junior medical staff to "screen" patients within the accident and emergency department rather than in the coronary care unit. In an attempt to reduce the delay of admission to the coronary care unit, we installed a telephone (with a number independent of the hospital switchboard) in the coronary care unit so that the nursing staff could accept for assessment any patients in whom the general practitioner suspected an acute myocardial infarction. We wrote to the general practitioners to explain the rationale for early referral and to tell them about the direct telephone line. We encouraged general practitioners to refer all patients with chest pain that might be caused by an acute myocardial infarction.

The procedure room at the back of the coronary care unit has a door into the hospital car park, which gives easy access for ambulances. If the procedure room is in use when a patient arrives at the coronary care unit the patient can be brought in through the front door of the coronary care unit into one of the beds in the unit. Although we expected some congestion at times, this was rare, and two patients never arrived together at the back door. The patients were assessed in the procedure room and the receiving medical registrar decided whether the patient should be kept in the coronary care unit, admitted to one of the general medical wards, or sent home.

We studied all patients who were referred in the first six months of the telephone system—that is from April 1987. In addition, we compared a subset of these patients who were admitted within six hours of the onset of symptoms with a second group, who despite the new system were referred to the accident and emergency department. Self referrals were not included in the analysis. We chose six hours because this is the cut off point in our unit for administration of thrombolytic treatment. We give thrombolytic treatment to all patients under the age of 70 with electrocardiographic evidence of acute myocardial infarction in whom there are no established contraindications.

Requests for reprints to Dr F G Dunn, Department of Cardiology, Stobhill General Hospital, Glasgow G21 3UW.

Accepted for publication 8 December 1988

At admission we noted the elements that accounted for the delay before thrombolysis. These were: the time from onset of symptoms until the general practitioner was contacted; the time taken by the general practitioner to arrive at the patient's home; the interval between the arrival of the general practitioner and the admission of the patient to the coronary care unit. Because the benefits of thrombolytic treatment are greatest the earlier it is administered, we also looked at the number of patients admitted within three hours of the onset of symptoms in both groups.

We compared the time differences between the two groups by a Mann-Whitney U test and the difference in numbers receiving thrombolytic treatment by χ^2 analysis.

Results

There was a steady decline in the use of the direct telephone line after the first month. So at the end of the third month we sent a second letter with a label with the telephone number on it. After this, use of the telephone line again increased. A total of 100 patients were referred via this system and 65 were kept in the coronary care unit. Thirty seven of the 65 were subsequently found to have had an acute myocardial infarction. Of the remaining 35 patients, 30 were transferred to the general medical wards, three were discharged home, and two were diverted to another hospital en route. Of the 30 patients transferred to the general medical wards, six had a discharge diagnosis of acute myocardial infarction, seven of unstable angina, eight of chest pain of uncertain cause, three of cardiac failure, two of syncope of uncertain cause, two of pneumonia, and one each of pulmonary embolism and cholecystitis. Review of the discharge records of these patients showed that hospital admission was required in each case, and therefore it appeared that the direct admission policy did not result in unnecessary admissions. Of the 65 patients admitted directly to the coronary care unit, 55 had pain lasting less than six hours, and we compared this group with 32 patients admitted from the accident and emergency department over the same period.

Figure 1 shows the various components of delay in admission. A major component was the interval from the onset of symptoms until the general practitioner was contacted, and this was similar in patients admitted directly to the coronary care unit and in those admitted to the accident and emergency department. Nor was there any significant difference between the groups in the time taken for the general practitioner to arrive. There was, however, a significant difference between the interval from the arrival of the general practitioner and subsequent admission to the coronary care unit. In patients admitted via the accident and emergency department, the mean time to admission was 1 hour and 32 minutes (range 25 minutes to 3 hours 40 minutes) and in the group admitted directly to the coronary care unit the mean time was 43 minutes (range 5 minutes to 2 hours) ($p < 0·001$).

The percentages of patients in whom acute myocardial infarction was confirmed were similar in the two groups (19 (59%) in the accident and emergency group and 31 (56%) in the direct admission group). A similar pattern of delay was seen in patients with acute myocardial infarction, with reduction from 1 hour 25 minutes (range 25 minutes to 3 hours 50 minutes) in the accident and emergency group to 41 minutes (range five minutes to one hour 40 minutes) in the directly referred group ($p < 0·001$).

Of the patients with acute myocardial infarction, 15 of the 31 admitted directly to the coronary care unit received thrombolytic treatment compared with three out of 19 in the accident and emergency group

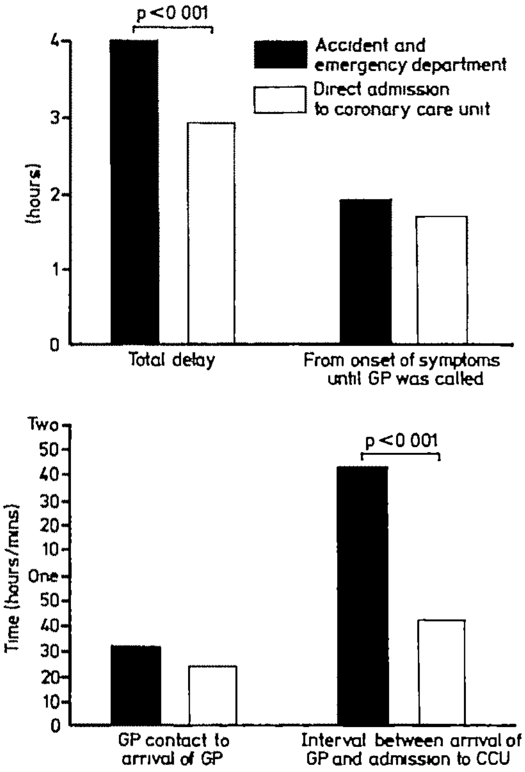


Fig 1 *Delay of patients admitted to the coronary care unit within six hours of the onset of chest pain by either the direct telephone route or via the accident and emergency department.*

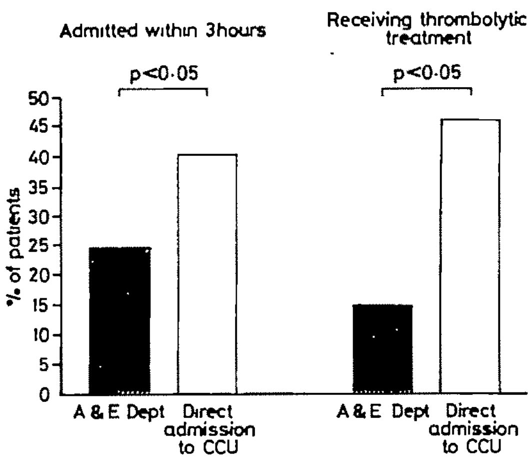


Fig 2 *Percentage of patients in each group who were admitted within three hours of the onset of symptoms and percentage of those with myocardial infarction who received thrombolytic treatment.*

(p < 0·05). A total of 31 patients (13 of whom received thrombolytic therapy) were admitted within three hours of the onset of symptoms—23 in the directly referred group (42%) and eight in the accident and emergency group (25%) (p < 0·05, fig 2).

Discussion

Early intervention with thrombolytic treatment both improves mortality and limits the extent of myocardial damage in acute myocardial infarction.[1,2] Thrombolysis is of most benefit when it is given early. Thus in an Italian study intravenous streptokinase given within an hour of onset of symptoms improved survival by 46% compared with an improvement of 17% in the treatment group as a whole.[1] This reinforces the need to look at the different components of the delay before the start of specialised medical help. The biggest single reason for exclusion from thrombolytic treatment is delay in reporting of symptoms.[3] We confirmed that the major source of delay is in the reporting of symptoms. This seems considerably shorter than that reported in a previous study for Glasgow.[5] These studies are not strictly comparable, however, because the previous study was in a different area of the city, was undertaken 10 years before, and included patients in whom symptoms had developed more than six hours before admission. The time to reporting of symptoms remains the major source of delay, but it is doubtful whether much impact can be made on this. Public education programmes could be considered, but it is unlikely this will modify what is often an instinctive pattern of behaviour.[6] Also we doubt whether the time taken by the general practitioner to arrive at the patient's home can be reduced. General practitioners have been equipped with defibrillators in an attempt to bring coronary care to the patient at an earlier stage.[7] But 18 months afterwards only 57% were still carrying their defibrillators regularly while on call.[8] Thrombolytic treatment might be given by general practitioners or the ambulance crew. Mobile coronary care units are successfully used in Belfast,[9] and may provide the best way of administering thrombolytic treatment in the community. The administration of thrombolytic treatment in the community is being assessed.[10]

At present most patients admitted with acute myocardial infarction are first referred to the accident and emergency department, which is often an unsatisfactory place for the immediate management of such patients.[4] They are generally seen, first by junior house officers, who may be slow to diagnose an infarct and to offer effective pain relief. Direct referral of patients to the coronary care units not only reduces the delay but it also leads to the patients being treated more quickly and efficiently by medical and nursing staff trained in coronary care.

We encountered few practical problems when patients were referred directly to the coronary care unit. All patients were fully assessed in the reception area in coronary care unit and were then admitted to the coronary care unit or to one of the medical wards as appropriate. Occasionally the patient was sent home (2% of the total number of referrals). Thirty seven of the total of 100 directly referred patients were subsequently shown to have acute myocardial infarction. The main problem with this policy is the need to keep reinforcing its use by the local general practitioners, because over the months enthusiasm wanes.[8]

The key aspect of such a method of reducing delay is its effect on the numbers of patients who are suitable for thrombolytic treatment. We found a significant increase in the number of patients admitted within three hours of the onset of symptoms when benefit from thrombolytic treatment is greatest, and also in those who received thrombolytic therapy on admission to the coronary care unit. The differences in the numbers who received thrombolytic treatment indicate that the recruitment rate for this treatment can be enhanced by a policy of direct admission to the coronary care unit.

The major delay in patients with acute myocardial infarction remains in the reporting of symptoms. Referral via the accident and emergency department is a major source of avoidable delay that can be eliminated by a policy of direct admission. This policy significantly reduced the delay in admission to the coronary care unit and increased the proportion of patients who were suitable for and most likely to benefit from thrombolytic treatment.

References

1 Gruppo Italiano per lo Studio della Streptocochinasi Nell' Infarcto Miocardio (GISSI). Effectiveness of thrombolytic therapy. *Lancet* 1986;i:397–402.

2 Simoons ML, Serruys PW, Van der Brand M, *et al.* Early thrombolysis in acute myocardial infarction. limitation of infarct size and improved survival. *J Am Coll Cardiol* 1986;7:717–28.

3 Jagger JD, Murray RG, Davies MK, Littler WA, Flint EJ. Eligibility for thrombolytic therapy in acute yocardial infarction. *Lancet* 1987;i:34–5.

4 Julian DG, Pentecost BL, Chamberlain DA. A milestone for myocardial infarction. *Br Med J* 1988,297:497–8.

5 Dunn FG, Elms S, Melville DI, Lawrie TDV, Murray TS. Early treatment of myocardial infarction in the community *Br Med J* 1978;ii:1143–5.

6 Rawles JM, Haites NE. Patient and general practitioner delays in acute myocardial infarction. *Br Med J* 1988;296:882–5.

7 Pai GR, Haites NE, Rawles JM. One thousand heart attacks in Grampian: the place of cardiopulmonary resuscitation in general practice. *Br Med J* 1987;294:352–4.

8 Rawles JM. General practitioners' management of acute myocardial infarction and cardiac arrest: relevance to thrombolytic therapy. *Br Med J* 1987;295:639–40.

9 Pantridge JF, Geddes JS. A mobile coronary care unit in the management of myocardial infarction. *Lancet* 1967;ii.271–3.

10 Weiss AT, Fine FG, Applebaum D, *et al.* Pre-hospital coronary thrombolysis: a new strategy in acute myocardial infarction. *Chest* 1987;92:124–8.

Br Heart J 1989;**61**:326–30

Use of a hollow wire to facilitate angioplasty of occluded vessels

L D R SMITH, D KATRITSIS, M M WEBB-PEPLOE

From the Department of Cardiology, St Thomas's Hospital, London

SUMMARY An USCI 0·038 inch (0·97 mm) floppy tipped hollow wire was used to facilitate the passage of angioplasty guide wires across severe stenoses or vessel occlusions before balloon angioplasty. The hollow wire was passed through a standard 7 or 8 French gauge Judkins coronary catheter to establish whether the obstruction could be breached. This reduced the cost of failure because angioplasty guiding systems were not committed to procedures that were unlikely to be successful. The hollow wire provides stability for the passage of the guide wire and can be used to measure distal pressure and inject contrast. To date it has been used in a total of 15 cases of occluded vessels; it failed to cross the lesion in four cases. Successful angioplasty followed in all patients in whom the lesion was crossed.

Although primary success rates in percutaneous transluminal coronary angioplasty, even for multiple lesions and multivessel disease,[1] are increasing, inability to cross the lesion remains a common cause of failure. Failure to cross a lesion is greatest with near or complete occlusion of a vessel. Because steerable balloon guide wires have floppy flexible tips to prevent local trauma it is difficult to apply appropriate force to cross the lesion with them.

Usually support for the balloon guide wire is increased by a balloon catheter, which can be advanced over the guide wire up to the proximal end of the stenosis or occlusion. The balloon catheter provides a stiffer, more stable platform from which to advance the wire, enabling more force to be delivered to the wire. Often, however, the inflexibility of the balloon prevents the force being applied in the right direction, and this is a critical factor in success. Even when the occlusion is crossed with the wire it may still be difficult or impossible to advance even an ultra-low profile balloon through the very small pathway. Furthermore, the use of a balloon involves a guiding catheter, balloon catheter, and balloon guide wire and the high failure rate[2] means that expensive equipment is wasted if the lesion cannot be crossed. We describe a simple and inexpensive alternative that does not require a guiding system or balloon catheter and we report our experience of its use.

Patients and methods

We used a USCI 0·038 inch (0·97 mm) straight hollow wire with a flexible tapered tip (USCI catalogue number 006200 (fig 1). This hollow wire can be passed through a routine 7 or 8 French left or right Judkins' catheter and a balloon guide wire can in turn be passed through the hollow wire. If this guide wire crosses the lesion, angioplasty can be attempted and the hollow wire and coronary catheter can be exchanged for a guiding system and balloon catheter. For such an exchange either an exchange wire or a spliceable wire is needed. We have most commonly used a Schneider Medintag* Kaltenbach 0·012 inch (0 30 mm) exchange wire (Schneider Medintag AG, lot number 30 003) with a J tip.[3] The hollow wire will take the 0·014 inch (0·36 mm) version of the Kaltenbach wire but the small swelling at the tip of this size Kaltenbach wire is too large to pass into the hollow wire, so it cannot be exchanged without removing the ensemble.

The hollow wire was packed with an internal stiffening wire core that was removed before use. A screw-on accessory can be attached to allow flushing of the lumen, to lubricate movement of the guide wire. The Kaltenbach wire was threaded into the hollow wire until the tip was sheathed within the floppy end of the hollow wire. The Kaltenbach

Requests for reprints to Dr L D R Smith, Department of Cardiology, St Thomas's Hospital, London SE1 7EH.

Accepted for publication 13 December 1988

---

*Now Schneider Shiley

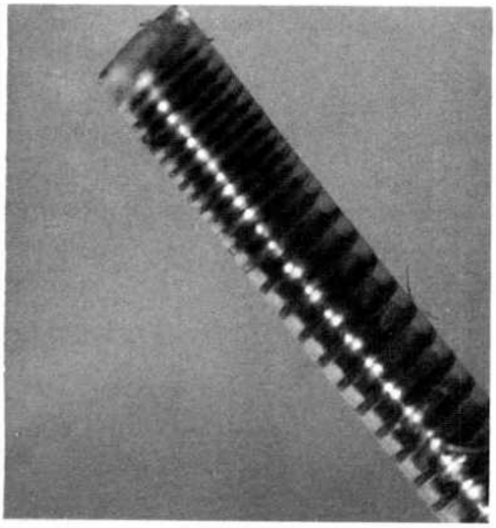


Fig 1 *The tip of the USCI 0·038 inch (0·97 mm) hollow wire (catalogue number 006200) magnified 24 times. Guide wires of 0·012 (0·30 mm) and 0·014 (0·36 mm) inches easily pass through it.*

wire-hollow wire ensemble was passed through a Tuohy-Borst haemostatic valve (ACS catalogue number 23242) and connected to the end of the diagnostic Judkins catheter that had been introduced into the femoral artery in the usual way via a short sheath. The side port of the haemostatic valve is attached to a manifold to allow pressure to be recorded or contrast injected through the Judkins catheter. The diagnostic catheter was engaged in the appropriate coronary artery ostium and the hollow wire and Kaltenbach wire were advanced to near the tip of the catheter. The Kaltenbach wire was then advanced along the appropriate artery to the occlusion with use of a torqueing tool if necessary. The hollow wire was then advanced very close to the tip of the Kaltenbach wire which could then be advanced further into the occlusion, with its tip protruding only one or two millimetres from the tip of the hollow wire. For every advance of the guide wire the hollow wire was further advanced, constantly providing support for the very delicate Kaltenbach tip. If the Kaltenbach wire successfully crossed the occlusion the hollow wire was usually able to follow it (fig 2). Then the guide wire could be removed and, after attachment of the screw-on flushing accessory, the hollow wire could be used to record distal pressure and to inject contrast into the distal vessel to show its appearance.

With the hollow wire still in situ across the lesion the Kaltenbach wire was replaced and the diagnostic Judkins catheter exchanged on the Kaltenbach wire-hollow wire ensemble with an appropriate guiding system. We found that this exchange was easier with the Kaltenbach wire-hollow wire ensemble than with the Kaltenbach wire alone since the increased stiffness prevents sudden displacement of the wire. This was especially true of the right coronary artery and graft angioplasty when it can be difficult to position securely the guiding catheter in the vessel orifice. When the guiding catheter was in place the hollow wire could be removed, leaving the Kaltenbach wire down the vessel. An appropriate balloon catheter was then advanced over the Kaltenbach wire. This invariably needs to be a balloon with an ultra-low profile because of the severity of the lesions underlying occlusion. Angioplasty then followed in the usual way.

Results

Between April and December 1987 we attempted percutaneous transluminal coronary angioplasty in 15 patients with chronic complete vessel occlusion. Two patients of the 15 had occlusions that were less than three weeks old and all but three occlusions had been present for more than four months. The mean time from presumed occlusion (on historical grounds) to angioplasty for all patients was five and a half months (range 3 weeks to 12 months) (failures, 10 months; successes, 4 months). Patients (13 men, two women) were aged between 41 and 70 years old (mean 53).

The sites of the lesions attempted were: nine in the left anterior descending coronary artery, one in the circumflex artery, three in the right coronary artery, and two in grafts. The table shows the results. In two patients (1 and 3) occlusion had not long been present

Table *A summary of the results of angioplasty of vessel occlusions by the hollow wire*

Case	*Sex*	*Age*	*Vessel occluded*	*Duration (mnth)*	*Outcome*	*Residual stenosis (%)*
1	M	46	RCA	< 1	Success	0
2	M	46	LAD graft	7	Success	50 (large graft)
3	M	50	RCA	< 1	Success	40
4	M	70	RCA	12	Failed	100
5	M	58	LAD	1	Success	10
6	M	67	LAD graft	6	Failed	100
7	F	62	LAD	9	Success	0
8	M	52	Cx	5	Success	0
9	M	47	LAD	2	Success	30
10	M	41	LAD	12	Failed	100
11	F	52	LAD	10	Failed	100
12	M	50	LAD	5	Success	10
13	M	55	LAD	4	Success	0
14	M	51	LAD	5	Success	20
15	M	56	LAD	5	Success	30

RCA, right coronary artery; LAD, left anterior descending coronary artery; Cx, circumflex.

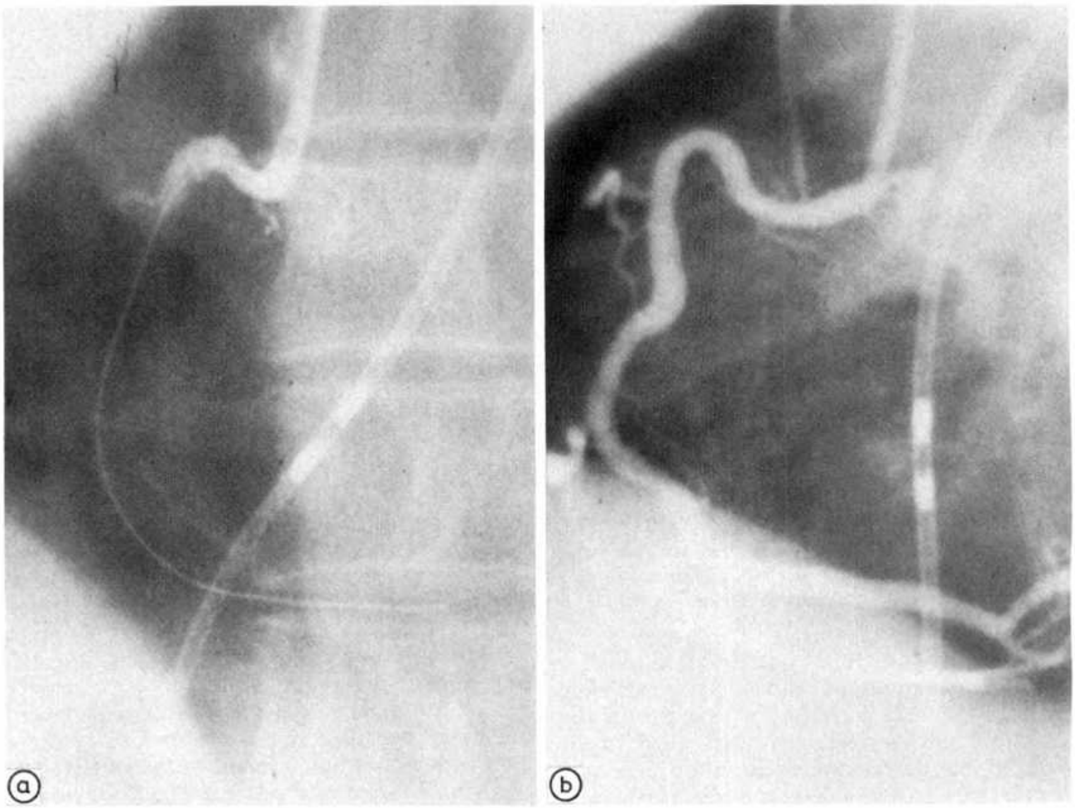


Fig 2 *(a) The hollow wire passed through an occlusion of the proximal right coronary artery and on to the distal vessel. The tip of the Kaltenbach wire protrudes approximately one centimetre from the tip of the hollow wire. (b) The same right coronary artery after angioplasty of the proximal lesion.*

and there was angiographic evidence of recent thrombus. In both these patients intracoronary thrombolysis (urokinase in patient 1 and streptokinase in patient 2) was used after initially breaching the occlusion. The results of successful breaching of the occlusion and angioplasty of the right coronary artery are shown in fig 2, while the left anterior descending artery is shown in fig 3.

OTHER USES OF THE HOLLOW WIRE

Contrast medium can be injected down the hollow wire to image the distal vessel. After removal of the Kaltenbach wire contrast can be injected through the hollow wire to delineate the distal artery.

We used the hollow wire to aid in the positioning of guard wires when we attempted lesions that affected side branches. Figure 3, showing two wires in position, is an example where the hollow wire was used to help to negotiate a severe stenosis of the left anterior descending artery that affected an important diagonal vessel. Initially a Kaltenbach guard wire was used and positioned in the diagonal branch. The left anterior descending coronary artery was then dilated by a spliceable J wire and a 20 mm by 35 mm balloon.

COSTS

We originally used the hollow wire to save money. When the lesion could not be crossed with the guide wire, the attempt could be abandoned without wasting a guiding catheter and balloon catheter. The advantage of this approach can be seen from the prices listed below:

USCI 0·038 inch hollow wire	£80
Schneider Medintag Kaltenbach exchange guide wire	£80
Guiding catheter	£80
Balloon catheter	£325
Ultra-low profile balloon	£475

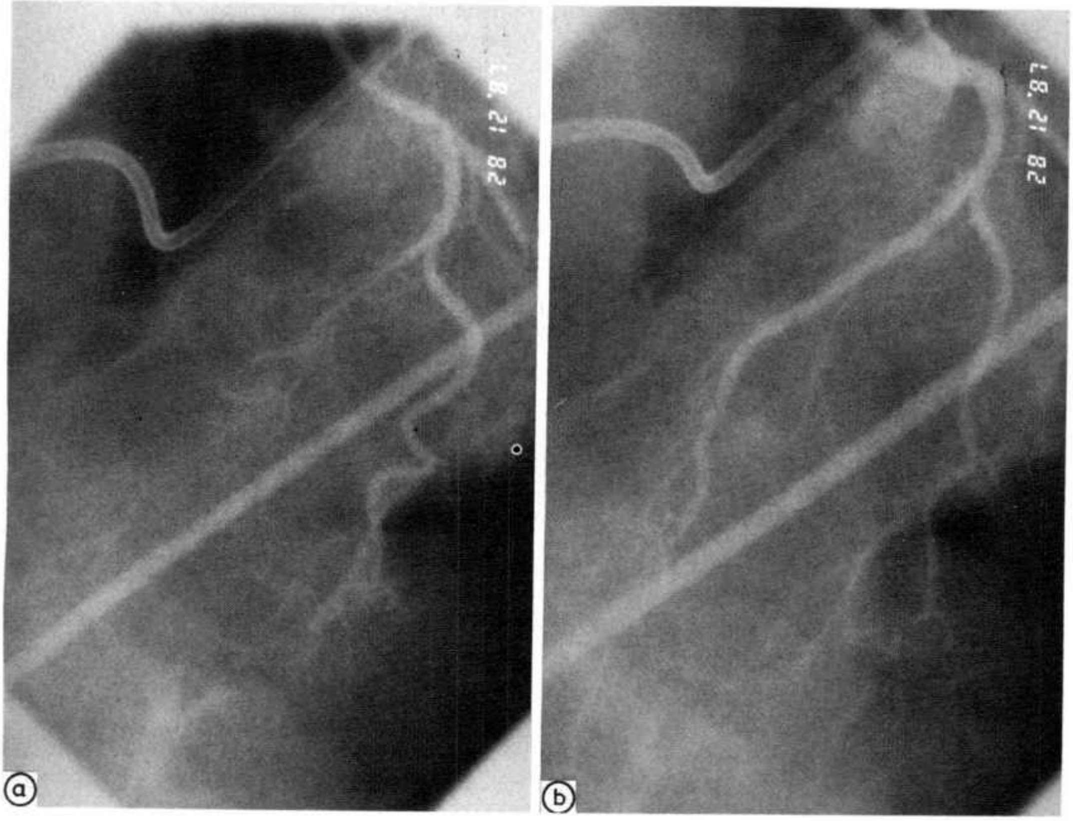


Fig 3 *(a) A left craniocaudal view of left anterior descending coronary artery occluded just distal to the first septal branch. (b) The left anterior descending artery after disobliteration and angioplasty showing no residual stenosis and good distal flow.*

Ordinary or high torque floppy guide wire	£50–£150

It costs £160 to use the hollow wire compared with £465–£615 for the guiding catheter and balloon catheter.

Discussion

Angioplasty of complete vessel occlusion is an attractive alternative to bypass surgery and is being increasingly attempted. Evidence suggests, as might be expected, that the sooner after occlusion that angioplasty is attempted the higher the chance of success.[4] This is borne out in this small series in which the failures occurred with the oldest lesions and the most recent occlusions were easiest to reopen. We have shown a reasonable success rate with the older lesions, however. The success is to some degree attributable to the advantages of using the hollow wire. The hollow wire has several advantages: (*a*) it increases the support and therefore the "pushability" of the guide wire; (*b*) it is more manoeuvrable and flexible than a balloon catheter; (*c*) it can be used to record distal pressure and to inject contrast into the distal vessel; (*d*) it crosses the lesion and because it has a larger diameter than the guide wire it facilitates subsequent passage of a balloon catheter; (*e*) it provides more support than an ordinary guide wire on which to exchange guiding catheters; and (*f*) it can be used initially through 7 or 8 French coronary catheters thus reducing costs.

A recent publication reports a similar technique with a 2·5 French gauge coronary infusion catheter instead of a hollow wire in nine patients.[5] Like us, this group report on complete vessel occlusions not associated with acute myocardial infarction. The

P, 25,739

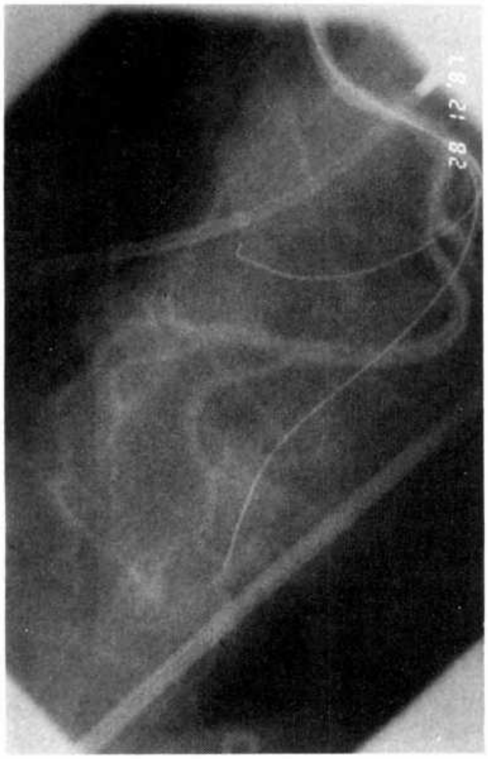


Fig 4 *A left anterior oblique view showing a Kaltenbach wire used as a guard wire positioned in the first diagonal branch and a spliceable J wire positioned in the left anterior descending artery.*

hollow wire has the advantage of being of smaller diameter and greater manoeuvrability than the infusion catheter but it cannot take guide wires greater than 0·014 inches (0·36 mm) in diameter.

We also recommend the use of the hollow wire in attempting angioplasty of subtotal occlusions and severe stenoses that are expected to be difficult to cross. The advent of detachable wire extensions may further reduce the cost of failure to cross the lesion.

References

1 Faxon DP, Kelsey S, Kellett MA, Ryan TJ, Detre K, and members of the NHLBI PTCA registry. Predictors of a successful angioplasty (NHLBI-PTCA registry) [Abstract]. *Circulation* 1986;**74**(suppl II):193.
2 Clark DA. Complex PTCA II: total occlusions. In: *Coronary angioplasty*. New York: Alan R Liss, 1987: 63–8.
3 Kaltenbach M. The long wire technique—a new technique for steerable balloon catheter dilation of coronary artery stenosis. *Eur Heart J* 1984;**5**:1004–9.
4 Wexman MP, Clark DA, Murphy MC, *et al*. Patient selection, complications and predictors of success in PTCA of total occlusion [Abstract]. *Circulation* 1986;**72**(suppl III):179.
5 de Swart JBRM, van Gelder LM, van der Krieken AM, El Gamal MIH. A new technique for angioplasty of occluded coronary arteries and by pass grafts, not associated with acute myocardial infarction. *Cathet Cardiovasc Diagn* 1987;**13**:419–23.

Br Heart J 1989;**61**:331–5

Effect of flosequinan on exercise capacity and symptoms in severe heart failure

J S ELBORN, C F STANFORD, D P NICHOLLS

From the Royal Victoria Hospital, Belfast

SUMMARY Twenty patients with severe chronic cardiac failure caused by ischaemic heart disease were treated with flosequinan 100 mg daily or placebo in addition to their existing treatment with diuretics and, in some, digoxin in a randomised double blind trial. After eight weeks of treatment, flosequinan significantly improved treadmill exercise time, increased peak achieved oxygen consumption, and improved the New York Heart Association symptom grade when compared with placebo. One patient in the placebo group died and another was withdrawn because heart failure worsened. One patient in the flosequinan group was lost to follow up but there were no other withdrawals.

Flosequinan was well tolerated with few adverse effects, and it may prove to be a useful addition to diuretics and digoxin in the treatment of chronic cardiac failure.

Chronic cardiac failure is a disabling disease with a high mortality.[1] Vasodilator treatment, when used in addition to diuretics, may relieve symptoms[2] and help to reduce mortality.[3,4] Flosequinan (7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone, Boots) is a new vasodilator that acts directly on both arterial and venous sites.[5] Previous studies have indicated that it may be of value in the treatment of chronic cardiac failure.[6-8]

We compared the effects of flosequinan and placebo on exercise performance and symptoms in a group of patients with severe chronic cardiac failure caused by ischaemic heart disease in whom symptoms had persisted despite diuretic treatment.

Patients and methods

PATIENT SELECTION

Twenty patients with chronic cardiac failure were considered for the study. Their symptoms and treatment had been stable for at least eight weeks. All the patients had dyspnoea or fatigue on exertion (New York Heart Association grade III or IV) despite treatment with at least 80 mg of frusemide or bumetanide 2 mg daily, a cardiothoracic ratio on a chest radiograph of $> 0{\cdot}55$, and a left ventricular ejection fraction (measured by radionuclide angiography) of $< 45\%$. Patients were excluded if exercise was limited by factors other than cardiac dyspnoea or fatigue. Other reasons for exclusion included primary valvar heart disease, hypertension, primary pulmonary disease, renal or hepatic impairment, recent myocardial infarction, or the use of cardioactive drugs other than digoxin and diuretics. All patients gave written informed consent to the study, which had been approved by the ethics committee of the Queen's University of Belfast.

STUDY METHODS

Diuretic treatment was continued unchanged throughout the trial. Seven patients receiving digoxin were also asked to continue at constant dose. During an initial single blind run-in phase on placebo that lasted at least four weeks, patients were exercised on several occasions every two weeks until their exercise duration varied by less than 10%. The tests on a treadmill were symptom-limited and a modified Naughton protocol was used (table 1). Throughout each test oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were measured by on line expired gas analysis with a paramagnetic analyser and infrared spectrometer respectively (PK Morgan Ltd).

At entry into the study we measured the patients' resting left ventricular ejection fraction and exercise capacity (treadmill time and peak achieved $\dot{V}O_2$) and we assessed their symptoms by the New York Heart

Requests for reprints to Dr D P Nicholls, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA.

Accepted for publication 20 December 1988

Table 1 *Modified Naughton exercise protocol used to test patients with heart failure*

Time (min)	*Speed (km/h)*	*Incline (%)*
4	1·6	0
8	2·4	0
12	3·2	0
16	3·2	3·5
20	3·2	7·0
24	3·2	10·5
28	3·2	14
32	3·2	17·5

Association grading. Patients answered a questionnaire on symptoms of dyspnoea and fatigue and were then randomly allocated in consecutive pairs to receive either flosequinan 100 mg daily or a matched placebo. Exercise testing and symptom assessment were repeated after two and eight weeks of treatment, and left ventricular ejection fraction was measured at eight weeks. Blood pressure and heart rate (supine and erect), New York Heart Association symptom grade, and body weight were recorded every two weeks.

STATISTICAL ANALYSIS

Throughout the trial an independent observer constructed a sequential analysis plan by studying the patient pairs in chronological order.[9] A preference was marked on the plot if at least two of the following percentage differences from baseline were seen between the two patients: exercise time ± 20% or more, peak $\dot{V}O_2$ achieved during exercise ± 20% or more, New York Heart Association symptom grade ± one subclass. If no preference was found, no mark was made. If a patient withdrew for a treatment related reason (increasing symptoms, side effects, or death) a preference for the other treatment was noted. The plan had an overall two sided significance level (α) of 0·05 and a power ($1 - \beta$) of 0·95, when it was assumed that the ratio of preferences between the treatments was 0·95:0·05.

On completion of the study we analysed exercise time, peak achieved $\dot{V}O_2$, left ventricular ejection fraction, and New York Heart Association grade in a fixed sample size design, using Wilcoxon's signed rank test for comparisons within groups and the Mann-Whitney test for comparisons between groups ($p < 0·05$ was regarded as significant). In each case, changes from baseline during treatment were compared between the groups rather than the absolute values, and all available data were used at each time point. Blood pressure, heart rate, and body weight were compared by analysis of covariance with repeated measures.

Results

The trial was stopped when seven preferences in favour of the active drug had been noted. The upper boundary on the sequential analysis plan had been reached after six patient pairs had completed week 8 ($p < 0·05$) (fig 1), but the final pair were allowed to complete the trial. To reach this point, ten patient pairs had been entered. In three pairs, no preference could be determined; in no pair was placebo preferred. In one pair (no 1) the patient on placebo developed an inflammatory arthritis and withdrew from the trial. This did not count as a preference for active drug. In another pair (no 5) the patient on placebo died after an episode of ventricular tachycardia, but the patient on active drug was lost to follow up, so no preference could be determined. In the third pair (no 8) the differences between the two patients were not great enough (exercise time + 8% and peak achieved $\dot{V}O_2$ − 1% in favour of active treatment, New York Heart Association grade improved on active treatment but deteriorated on placebo treatment). In addition, one patient on placebo (no 2) withdrew because of deterioration of

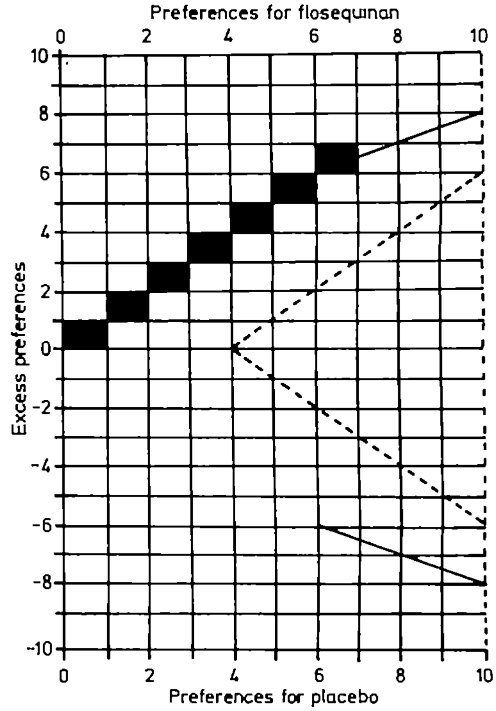


Fig 1 *Sequential analysis plan for active treatment (flosequinan) against placebo. Significance level 5%. Power 95% to predict a proportion of preferences of 0 95:0 05.*

Table 2 *Details of patient pairs on entry (week 0) into the study*

Pair no	*Age (yr)*	*Duration of disease (yr)*	*NYHA grade*	*LVEF (%)*	*Diuretic/digoxin dose (daily)*	*Other treatment (daily)*
1 F	38	1 5	IIIb	18	Fr 120 mg A 15 mg	
P	63	4	IV	20	Fr 80 mg D 125 μg A 10 mg	Al 100 mg M 1500 mg
2 F	69	3	IIIb	24	B 3 mg A 15 mg	W 3 mg
P	62	3	IIIb	30	Fr 120 mg A 15 mg	
3 F	59	4	IIIa	27	Fr 80 mg A 10 mg	W 5 mg P 75 mg
P	68	2	IIIa	27	Fr 80 mg A 10 mg	
4 F	51	2	IIIa	18	Fr 80 mg A 10 mg D 250 μg	W 9 mg Am 200 mg
P	56	3	IIIb	18	Fr 80 mg A 10 mg D 125 μg	W 5 mg
5 F	52	4	IIIb	42	Fr 80 mg A 10 mg	
P	71	7	IIIb	37	Fr 80 mg A 10 mg	
6 F	69	4	IV	18	Fr 80 mg A 10 mg	
P	66	0 5	IIIb	24	Fr 80 mg A 10 mg D 125 μg	
7 F	66	4	IIIb	33	Fr 120 mg A 15 mg D 125 μg	W 3 mg
P	58	3	IIIb	31	Fr 120 mg A 15 mg	
8 F	59	4	IIIb	23	Fr 80 mg A 10 mg	C 800 mg
P	63	1 5	IIIb	30	Fr 80 mg A 10 mg	
9 F	66	4	IIIb	25	Fr 80 mg A 10 mg D 125 μg	
P	72	4	IIIa	23	Fr 80 mg A 10 mg	
10 F	66	1	IIIb	36	Fr 80 mg A 10 mg	
P	62	2	IIIa	21	Fr 80 mg A 10 mg	
Mean (SD) F	59 (10)	3 1 (1 2)	IIIb†	27 (8)	Fr* 92 (19) mg A 12 (4) mg	
P	64 (5)	3 0 (1 7)	IIIb†	26 (6)	Fr* 92 (19) mg A 11 (2) mg	

*Assuming 1 mg bumetanide ≃ 40 mg frusemide.
†Median
F, flosequinan; P, placebo, Fr, frusemide, B, bumetanide; A, amiloride; D, digoxin, Al, allopurinol; M, metformin, P, prothiaden, Am, amiodarone, C, cimetidine, W, warfarin; LVEF, left ventricular ejection fraction

his symptoms; this was counted as a preference for active drug.

All the patients studied were men (table 2) and had electrocardiographic evidence of previous myocardial infarction. Two patients in each group had a previous history of hypertension. Table 3 shows the absolute values for exercise time, peak achieved $\dot{V}O_2$, left ventricular ejection fraction, and New York Heart Association symptom grade. Baseline exercise time and peak achieved $\dot{V}O_2$ were greater in the group on active treatment than in the placebo group but these differences were not significant. There were no significant improvements in either exercise time or peak achieved $\dot{V}O_2$ during placebo treatment, but significant increases were seen after two weeks of treatment with flosequinan, which continued to eight weeks (table 3). Mean exercise time improved over baseline by 230 seconds (95% confidence interval 88·4 to 538 2 s) at week 2 and by 243 (83·2 to 404·6) seconds at week 8, compared with changes on placebo of − 71 (− 144·3 to 2·3) seconds and − 84 (− 197·5 to 28·7) seconds respectively. Peak achieved $\dot{V}O_2$ on flosequinan was 2·5 (0·9 to 4·1) ml/min/kg higher than baseline at week 2 and 2·4 (0·8 to 4·0) ml/min/kg

Table 3 *Response to flosequinan and placebo (mean (95% confidence interval))*

	Flosequinan			*Placebo*		
	Week 0 *n = 10*	*Week 2* *n = 10*	*Week 8* *n = 9*	*Week 0* *n = 10*	*Week 2* *n = 9*	*Week 8* *n = 7*
Exercise time (s)	866 (550–1182)	1079* (802–1357)	1120* (780–1459)	666 (465–866)	631 (393–868)	669 (419–920)
Peak achieved $\dot{V}o_2$ (ml/min/kg)	16·5 (13·6–19·4)	19·0* (15·8–22·2)	18·7* (15·0–22·4)	13·3 (12·2–14·4)	13·6 (11·4–14·6)	13·5 (12·9–14·3)
Left ventricular ejection fraction (%)	27·4 (21·2–33·8)	—	30·0 (23·1–36·9)	26·1 (21·8–30·4)	—	23·8 (14·6–33·0)
New York Heart Association symptom grade (median)	IIIb	IIIa*	IIb*	IIIb	IIIb	IIIb (n = 8)

*p < 0·01 *v* baseline (Wilcoxon paired test)

at week 8; whereas on placebo the changes were − 0·7 (− 2·3 to 0·9) ml/min/kg and − 0·5 (− 1·5 to 0·9) ml/min/kg respectively. There was a small increase in left ventricular ejection fraction during treatment with flosequinan (4·1 (− 0·1 to 8·3) % at week 8), while the change on placebo was − 0·5 (− 9·2 to 8·2) %. Figure 2 shows the significance values for these changes. There was no change in New York Heart Association symptom grade after placebo, whereas symptoms progressively improved from a median value of IIIb to IIIa at two weeks ($p < 0·01$) and to IIb at eight weeks ($p < 0·001$) during treatment with flosequinan.

There were small reductions in body weight after both treatments; neither was significant. Blood pressure at rest, standing, and at maximum exercise was unchanged by both treatments. There were significant changes in resting and standing heart rate. During placebo treatment, supine heart rate fell from a mean value of 80·9 to 72·6 beats/min at week 8, whereas during treatment with flosequinan heart rate increased from 80·1 to 90·7 beats/min. The difference between the treatments was significant (p = 0·001). Standing heart rate fell from 88·3 to 79·0 beats/min on placebo, and increased from 91·4 to 102·0 beats/min on flosequinan (difference p = 0·004). A small increase in peak exercise heart rate was also seen after flosequinan, but this was not significant. Symptoms of breathlessness, reported on a patient questionnaire, were improved after flosequinan (p = 0·002 *v* placebo), as were those of fatigue (p = 0·02 *v* placebo).

There were no serious adverse effects on placebo (other than those noted above) that necessitated withdrawal from the trial. While on flosequinan, one patient had an episode of wheezing which promptly responded to inhaled β_2 agonists; he had suffered intermittent wheezing for many years. Another had effort syncope, but this was found to be caused by hypoglycaemia.

Discussion

Peripheral vasoconstriction is a prominent feature of the vascular response to chronic cardiac failure.[10] Vasodilator drugs reduce cardiac afterload, preload, or both. Flosequinan is active at both arterial and venous sites,[5] but its precise mechanism of action is unknown. The action does not involve adrenoceptors or calcium channels, but may result from an increase in the level of membrane bound cyclic guanosine monophosphate.[11] Although vasodilatation is a logical treatment for chronic cardiac failure, the use of many such drugs has been limited by the development of tolerance.[12] Experience with prazosin indicates that attenuation of effect is seen after four to eight weeks of treatment.[13–15] The present study suggests that tolerance does not occur within eight weeks of treatment with flosequinan, because the

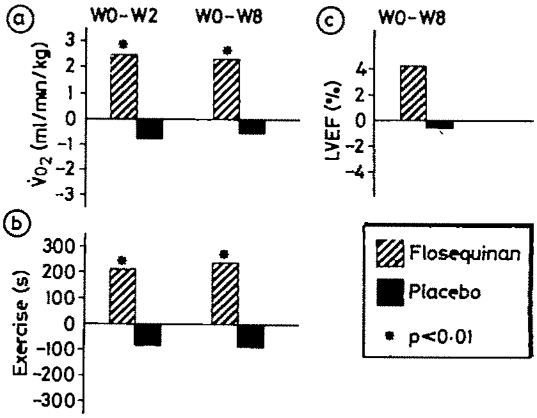


Fig 2 *Changes in mean (a) peak $\dot{V}o_2$ (ml/min/kg), (b) exercise time, and (c) left ventricular ejection fraction (%) in the flosequinan group compared with placebo at week 0 to week 2 and week 0 to week 8. *p < 0·01 (Mann-Whitney U test).*

weeks of treatment with flosequinan, because the beneficial effects recorded at two weeks were still seen after eight weeks of drug administration. However, longer term studies will be required to exclude the eventual development of tolerance.

Although many studies have shown favourable acute haemodynamic responses to vasodilator drugs, there are few longer term randomised controlled trials.[16] One limitation is the high mortality of the condition, which makes lengthy trials difficult to conduct. There also may be reluctance to include a placebo treated group in trials on patients with severe chronic cardiac failure, but we consider that a limited number of such trials should be conducted. In order not to prolong the trial beyond what is necessary to prove a difference, we used the sequential analysis technique to allow a continuous overview of trial progress.

Haemodynamic measurements and other standard indices of left ventricular performance (such as ejection fraction) correlate poorly with symptoms and exercise capacity in patients with chronic cardiac failure.[17 18] In contrast, exercise testing with measurement of respiratory gas exchange closely reflects symptoms[19 20] and is a reliable objective method of assessment of disease progress.[21] In the present study there was a significant increase in peak achieved $\dot{V}O_2$ during exercise after two weeks of active treatment, and this was sustained to eight weeks. No such improvement was seen after placebo, which would exclude a training effect associated with repeated exercise testing, even though the tests were infrequent. We also saw a significant improvement in symptom grade after active treatment.

There were few adverse effects, and the single death during the trial (on placebo) is not unexpected in a group of patients with severe chronic cardiac failure. We conclude that flosequinan may prove to be of value in the treatment of patients with diuretic resistant heart failure.

We thank Dr R Bratty, Dr R Wynne, and Mr D J McEntegart of the Statistical Department of the Boots Company for their advice and support. JSE was in receipt of a Royal Victoria Hospital research fellowship.

References

1 Wilson JR, Schwartz JS, Sutton M St J, *et al.* Prognosis in severe heart failure: relation to hemodynamic measurements and ventricular ectopic activity. *J Am Coll Cardiol* 1983;**2**:403–10.

2 Packer M. Vasodilator and inotropic therapy for severe chronic heart failure: passion and skepticism. *J Am Coll Cardiol* 1983;**2**:841–52

3 CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 1987;**316**:1429–35.

4 Cohn JN, Archibald DG, Ziesche S, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;**314**:1547–52.

5 Cowley AJ, Wynne R, Hampton JR. The effects of BTS 49465 on blood pressure and peripheral arteriolar and venous tone in normal volunteers. *J Hypertens* 1984;**2**(suppl 3):547–9.

6 Kessler PD, Packer M. Hemodynamic effects of BTS 49465, a new long-acting systemic vasodilator drug, in patients with severe congestive heart failure. *Am Heart J* 1987;**113**:137–43.

7 Silke B, Verma SP, Taylor SH. A haemodynamic and treadmill exercise study with flosequinan in mild chronic heart failure [Abstract]. *Br J Clin Pharmacol* 1987,**24**:250P–1P.

8 Cowley AJ, Wynne RD, Stainer K, Fullwood L, Rowley JM, Hampton JR. Flosequinan in heart failure. acute haemodynamic and longer term symptomatic effects. *Br Med J* 1988;**297**:169–73.

9 Armitage P. *Sequential medical trials.* Oxford: Blackwell, 1975.

10 Zelis R, Flaim SF. Alterations in vasomotor tone in congestive heart failure. *Prog Cardiovasc Dis* 1982; **24**·437–59

11 Allcock AA, Frodsham G, Sim MF. Effects of flosequinan, a novel arteriovenous dilating agent, on cGMP levels in rat isolated aortic strips [Abstract]. *Br J Pharmacol* 1988,**94**:430P

12 Colucci WS, Williams GH, Alexander RW, Braunwald E. Mechanisms and implications of vasodilator tolerance in the treatment of congestive heart failure. *Am J Med* 1981;**71**:89–99.

13 Colucci WS, Wynne J, Holman BL, Braunwald E. Long-term therapy of heart failure with prazosin: a randomized double blind trial. *Am J Cardiol* 1980; **45**:337–44.

14 Harper RW, Claxton H, Middlebrook K, Anderson S, Pitt A. The acute and chronic haemodynamic effects of prazosin in severe congestive cardiac failure. *Med J Aust* 1980;**ii**:(suppl):36–8.

15 Bayliss J, Norell MS, Canepa-Anson R, Reid C, Poole-Wilson P, Sutton G. Clinical importance of the renin-angiotensin system in chronic heart failure. double blind comparison of captopril and prazosin. *Br Med J* 1985;**290**:1861–5.

16 Lipkin DP, Poole-Wilson PA. Treatment of chronic heart failure: a review of recent drug trials. *Br Med J* 1985;**291**:993–6.

17 Franciosa JA, Park M, Levine B. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. *Am J Cardiol* 1981;**47**:33–9.

18 Elborn JS, Stanford CF, McNair W, Nicholls DP. Relationship of left and right ventricular ejection fraction to exercise capacity and symptom status in patients with chronic cardiac failure [Abstract]. *Clin Sci* 1987;**73**(suppl 17):23P.

19 Patterson JA, Naughton J, Pietras RJ, Gunnar RM. Treadmill exercise in assessment of the functional capacity of patients with cardiac disease. *Am J Cardiol* 1972;**30**:757–62.

20 Lipkin DP, Perrins J, Poole-Wilson PA. Respiratory gas exchange in the assessment of patients with impaired ventricular function. *Br Heart J* 1985; **54**:321–8.

21 Lipkin DP. The role of exercise testing in chronic heart failure. *Br Heart J* 1987;**58**:559–66.

Br Heart J 1989;**61**:336–43

Half time of the diastolic aortoventricular pressure difference by continuous wave Doppler ultrasound: a measure of the severity of aortic regurgitation?

STEIN O SAMSTAD, LARS HEGRENAES, TERJE SKJAERPE, LIV HATLE

From the Section of Cardiology, Department of Medicine, Regional Hospital, Trondheim, Norway

SUMMARY Thirty four patients with aortic regurgitation were studied by continuous wave Doppler ultrasound. In 30 of these the regurgitation was graded by cineangiography as mild, moderate, or severe and in four severe regurgitation was confirmed at operation. The half times of the aortoventricular pressure differences obtained with Doppler compared well with those obtained from pressure recordings at catheterisation. The relation between pressure half times and cineangiographic gradings of severity was not consistent. Similarly, a control group of patients without aortic regurgitation showed a wide range of the invasively recorded pressure half times which overlapped with those in patients with aortic regurgitation. This suggests that factors such as systemic vascular resistance, and aortic and left ventricular compliance can have an appreciable effect on the pressure half time. If these factors are not included the method will be of limited value, except in patients with pressure half times of < 300 ms, when regurgitation invariably is severe.

These results suggest that at present the method is of value only in recognising the patients with the most severe aortic regurgitation who need early operation.

Aortic regurgitation can be diagnosed with high sensitivity and specificity by pulsed and continuous wave Doppler ultrasound.[1 2] Provided the angle between the ultrasound beam and the regurgitant jet is small, the maximal jet velocities can be recorded with continuous wave Doppler and the instantaneous pressure difference between the aorta and the left ventricle can be calculated.[3] The decline of this gradient throughout diastole can then be measured non-invasively.[4-6]

The rate of decrease of the aortoventricular pressure difference during diastole obtained by pressure recording or non-invasively by continuous wave Doppler has been used as a measure of the severity of aortic regurgitation.[6-8] The rate of decline in this pressure difference, however, also depends on aortic compliance, total systemic vascular resistance, and the left ventricular compliance.[8] The rate of decrease of the pressure difference can be expressed by its pressure half time—that is the time from the peak pressure difference to a 50% decrease in that value.[7 9]

The aim of our study was to assess whether this pressure half time obtained from the maximal velocity of the aortic regurgitation recorded by continuous wave Doppler ultrasound was a useful measure of the severity of the aortic regurgitation. For this we studied (*a*) the agreement between the non-invasive and the invasive methods by comparing the half time of the pressure difference calculated from the maximal velocities of the aortic regurgitation with that obtained from the aortic and left ventricular pressure recordings at catheterisation; (*b*) we compared the pressure half time of the aortic regurgitation with the angiographic assessment of severity; (*c*) we noted the range of the half times of the diastolic pressure difference between the aorta and left ventricle measured at catheterisation in patients without aortic regurgitation; and (*d*) we examined the relation between the pressure half time and the systemic vascular resistance in patients with aortic regurgitation.

The effect of aortic compliance upon the pressure

Requests for reprints to Dr Stein O Samstad, Section of Cardiology, Department of Medicine, Regional Hospital, N-7006 Trondheim, Norway

Accepted for publication 30 August 1988

Table 1 *Data on patients with aortic regurgitation*

Patient No	*Age (yr)*	*Additional diagnoses*	*AG*	*HR (beats/min)*	*DPHT (ms)*	*IPHT (ms)*	*SVR (dyn s cm^{-5})*	*LVEDP (mm Hg)*
1	62		1+	52	702	550	1614	15
2	67	AS	1+	78	700	540	1717	14
3	58	MS, TR, TS	1+	68	623	760	1460	15
4	59	MR	1+	70	617	420		10
5	46	MS	1+	74	500	460	2026	4
6	59	AS, MS, MR	2+	46	600	540	3097	20
7	65	AS, IHD	2+	72	533	430	1800	16
8	45	MS, MR	2+	66	496	410	1513	12
9	60	AS	2+	66	460	390	1518	14
10	64	AS, MS	2+	96	450	400	3277	16
11	60		2+	78	440	470	793	18
12	67	MS	2+	108	390	260	3370	20
13	70	AS	2+	67	360	312	1496	30
14	45	AS	2+	74	358	370	1776	10
15	58	AS, MR, IHD	2+	71	353	340	818	8
16	65	MR, IHD	3+	49	670	650	3779	36
17	65	MS	3+	50	623	560	3333	12
18	68		3+	49	556	470	1275	14
19	55	DCM	3+	70	453	440	1990	32
20	45	AS	3+	66	405	500	1080	10
21	56	AS	3+	58	380	380	1096	28
22	49		3+	75	360	350	1150	10
23	66		3+	59	352	390	2249	36
24	45	AS	3+	77	350	310	2491	28
25	29		3+	67	320	240	753	20
26	55		3+	81	310	230	1383	24
27	46		3+	47	255	300	1194	18
28	39	MR	3+	82	240	300	1112	28
29	26		3+	90	215	160		20
30	67	IHD	3+	90	205	170	1909	22
31	58	AE	3+*	80	245			
32	37	PL	3+*	98	218			
33	46	AE	3+*	66	170			
34	40	AE	3+*	74	160			

AG, cineangiographic grading (1+ = mild, 2+ = moderate, and 3+ = severe aortic regurgitation; 3+* severe aortic regurgitation at operation (patients 31–34 not included in the study group)); DPHT, Doppler aortoventricular pressure difference half time, IPHT, invasive aortoventricular pressure difference half time; SVR, systemic vascular resistance, HR, heart rate; LVEDP, left ventricular end diastolic pressure; IHD, ischaemic heart disease; MR, mitral regurgitation; AS, aortic stenosis; MS, mitral stenosis; TR, tricuspid regurgitation, TS, tricuspid stenosis, DCM, dilated cardiomyopathy; AE, acute endocarditis; PL, paravalvar leak.

half time could not be evaluated because there was no method of recording this variable.

Patients and methods

PATIENTS (Table 1)

We studied 30 patients with aortic regurgitation admitted to the hospital during a two year period. Left heart catheterisation was done in all and 28 also had right heart catheterisation. Only patients who showed a distinct envelope of the maximal velocities of the aortic regurgitation on the Doppler recording were included in the study. Fifty nine per cent of the patients with angiographic evidence of aortic regurgitation were included in the study.

Eighty nine per cent of the patients with severe, 50% with moderate, and only 20% with mild regurgitation at angiography were included. The Doppler recordings were made within three days of the invasive study, usually the day before catheterisation. All recordings were analysed blindly after the end of the study.

In addition to the study group four patients with severe aortic regurgitation verified at operation were studied with Doppler ultrasound. These patients did not have catheterisation before operation.

The control group consisted of 30 patients without aortic regurgitation who had left heart catheterisation, including an aortic root contrast injection, for ischaemic heart disease (table 2).

DOPPLER ECHOCARDIOGRAPHY

Continuous wave Doppler recordings were made on an Irex System IIIB ultrasonograph with both a combined two dimensional and 2 MHz Doppler transducer and a non-imaging 2 MHz Doppler transducer. The maximal velocity of the aortic regurgitation was recorded from apical, parasternal, and suprasternal positions, and the recording with the highest velocity and best defined maximal velocity envelope was used for measurements.

A line was drawn along the maximal velocity envelope. Another line, parallel to the baseline, was then drawn at the velocity corresponding to the

Table 2 *Comparison between patients without aortic regurgitation and those with aortic regurgitation*

	Age (yr)	*HR (beats/min)*	*DPHT (ms)*	*IPHT (ms)*	*SVR (dyn.s.cm^{-5})*	*LVEDP (mm Hg)*
Control group (n = 30) (Mean (SD)):	57 (7)	59 (10)		613 (157)		14·3 (6·8)
Minimum	37	40		380		6
Maximum	67	78		910		30
Aortic regurgitation (Mean (SD)):						
Mild (n = 5)	58 (7)	68 (9)	628 (82)	546 (131)	1704 (239)	11·6 (4·7)
Moderate (n = 10)	59 (8)	74 (17)	444 (82)	392 (79)	1943 (967)	16·4 (6·2)
Severe (n = 15)	51 (13)	67 (14)	380 (144)	363 (141)	1771 (912)	22·5 (8·8)
Mild, moderate, and severe (n = 30)	55 (11)	69 (14)	445 (144)	403 (136)	1824 (851)	18·7 (8·4)
Severe at operation (n = 4)	45 (9)	79 (13)	198 (40)			

DPHT, Doppler aortoventricular pressure difference half time; IPHT, invasive aortoventricular pressure difference half time; SVR, systemic vascular resistance; HR, heart rate; LVEDP, left ventricular end diastolic pressure.

maximal velocity divided by 1·4. The pressure half time can then be measured along the baseline, from the time of maximal velocity and maximal aortoventricular pressure difference, to the point at which the second line crosses the maximal velocity envelope (fig 1).[9]

The decay in velocity is linear in patients with severe aortic regurgitation but it may be curvilinear in others. When diastole is too short for the two lines to cross before end diastole three different options for measurement of the pressure half time have to be considered (fig 2).

(*a*) A line drawn along the maximum velocity envelope can be prolonged beyond end diastole, but this is ambiguous in patients with a curvilinear velocity decay. The use of this method in such patients gives variable results with varying heart rate and diastolic length. The result varies depending on whether only the initial steeper part of the curve is present or, as with the slower heart rate, a less steep part is included in the recording.

(*b*) A straight line drawn through the maximal velocities in early and late diastole and with prolongation beyond the velocity envelope crosses the horizontal line of half the initial pressure difference either during diastole or after. This option is also liable to variation in pressure half time with varying heart rates and diastolic length.

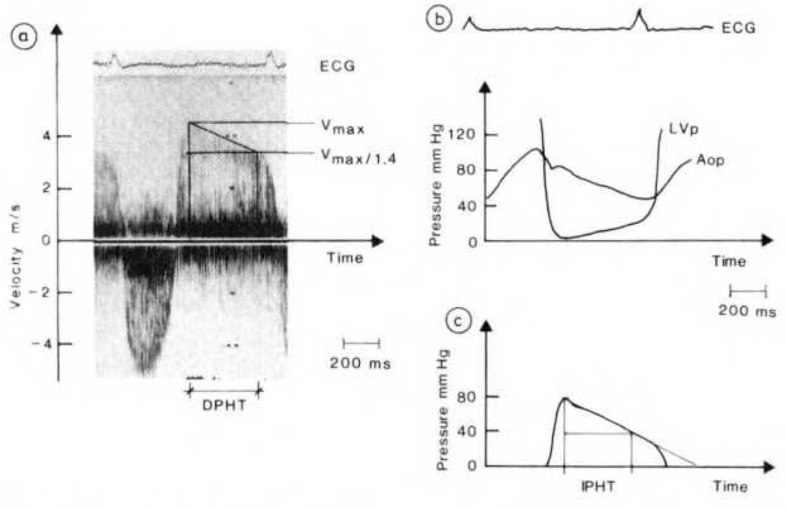


Fig 1 *Continuous wave Doppler echocardiogram and pressure recordings from patient 21 with combined aortic stenosis and regurgitation. The regurgitation was graded as severe (3+) at angiography. (a) Measurement of pressure half time from the Doppler recording (DPHT). (b) left ventricular (LV) and aortic (Ao) pressures recorded during pull back of the catheter are superimposed for beats with equal RR intervals. (c) Difference between the pressures during diastole and the invasively measured pressure half time (IPHT). The paper speed in the recordings was 50 mm/s.*

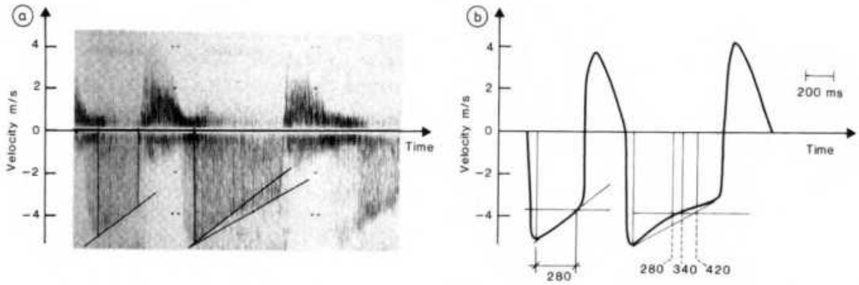


Fig 2 *(a) Aortic stenosis and regurgitation recorded by continuous wave Doppler from the right sternal border. The regurgitation is away from the transducer and is seen below the zero line. (a) Tracing of the maximal velocity of the regurgitation shows three options for measurement of the half time of aortoventricular pressure difference. (1) 340—the crossing point between the maximal velocity envelope and the velocity where the peak pressure difference is halved (that is the peak velocity divided by 1·4). (2) 420—the crossing point between a line drawn through the maximum and minimum diastolic velocities of the regurgitation jet and the velocity where the peak pressure difference is halved. (3) 280—the crossing point between a line along the initial slope of the maximal velocities and the velocity at which the aortoventricular pressure difference is halved.*

When the decrease in velocity is linear, as in the first diastolic period in (a) where the RR interval is short, all the methods gave a similar pressure half time (280 ms) whereas for the next beat with longer diastole and a curvilinear maximal velocity envelope the three methods give different results, 340, 420, and 280 ms respectively.

(*c*) A straight line drawn along the initial slope of the recorded maximal velocities from the aortic regurgitation is less susceptible to variations in heart rate than the other two options. Usually the initial part of the velocity decrease is linear and easy to define. This method may, however, distinguish less well between curves with an initially rapid but then slower velocity decay and curves where the velocity decay is rapid throughout diastole, as seen in patients with severe aortic regurgitation. Thus none of these methods is ideal.

In this study we measured the pressure half time from the Doppler recording along the maximum velocity of the curve whenever possible (fig 1). In patients with a linear velocity decay the line along the maximum velocities was extended beyond end diastole when necessary. In patients with a curvilinear velocity decrease we used a line extended along the initial slope (fig 2). The time duration from the peak velocity to the crossing point of the line along the maximal velocities and the line indicating half the initial pressure difference was defined as the Doppler pressure half time (DPHT). This was calculated on the basis of recordings from 4–6 beats.

CATHETERISATION

At left and right heart catheterisation pressures were recorded with fluid filled catheters connected to Elema 746 pressure transducers. The pressure difference between the aorta and the left ventricle was obtained by superimposing pressures recorded during pull back of the catheter from the left ventricle to the ascending aorta. Beats with comparable RR intervals were used.

Left ventricular end diastolic pressures were recorded as recommended by the report of the World Health Organisation/International Society and Federation of Cardiology Task Force on haemodynamics.[10] The fourth intercostal space in the anterior axillary line was used as zero level for pressure measurements.[11]

We used a modification of the pressure half time of diastolic pressure in the ascending aorta as described by Libanoff.[7] But unlike Libanoff, we included the left ventricular diastolic pressures in the calculation and used the same approach as for the non-invasive method (fig 1). A normal range of invasively measured pressure half times was obtained from the control group of cardiac patients without aortic regurgitation. Cardiac output was obtained by the Fick method and systemic vascular resistance was calculated in the 28 patients of the study group who had both left and right heart catheterisation[12] (table 1).

CINEANGIOGRAPHY

Cineangiographic views were taken in the anterioposterior projection of a bolus injection of 50 ml Isopaque (Nycomed, Oslo) at an injection rate of 18 ml/s into the ascending aorta. At examination of the cineangiographic films the regurgitations were graded according to Eie[13]:

No aortic insufficiency (0)—No regurgitation through the aortic valves could be shown.

Mild aortic insufficiency (1+)—Regurgitation of contrast medium could be seen midway down the left ventricular cavity and was then expelled in the following systole.

Moderate aortic insufficiency (2+)—Contrast could be seen down to the left ventricular apex and was expelled in the following systole.

Severe aortic insufficiency (3+)—Contrast medium was regurgitated down to the apex and was not expelled in the following systole, and there was opacification of an increased residual volume.

STATISTICAL ANALYSIS

Means (SD) were calculated for the data from the invasive and non-invasive recordings. The sample points from each patient were based on the average of the recordings from 4–6 heart beats. We tested the differences between the means of the samples in the subgroups (defined by angiographic grading) by the Bonferroni t test as described by Glantz.[14]

The agreement of measurement of the pressure difference half times between the two methods was analysed according to the method recommended by Bland and Altman.[15]

Results

Tables 1 and 2 give the results for the study group and the control group. Cineangiography showed mild aortic regurgitation in five patients, moderate regurgitation in 10, and severe regurgitation in 15.

COMPARISON OF PRESSURE HALF TIME MEASURED NON-INVASIVELY AND INVASIVELY

The difference in agreement between pressure half times measured at catheterisation and by Doppler was large both for the whole study group (limits of agreement from −106 ms to +184 ms) and for the subgroup of patients with severe aortic regurgitation (limits of agreement from 95 ms to +127 ms) (fig 3).

COMPARISON OF PRESSURE HALF TIME MEASURED NON-INVASIVELY AND ANGIOGRAPHIC GRADE

The pressure half times measured by Doppler were not significantly different in those with severe (mean pressure half time 385 (144) ms, range 205–670 ms) and moderate regurgitation (mean 444 (82) ms, range 353–600 ms), $p > 0.05$ (fig 4).

The mean pressure half times for mild regurgitation (628 (82) ms, range 500–702 ms) were significantly different from those associated with severe ($p < 0.05$) but not moderate regurgitation ($p > 0.05$). There was, however, wide variation within each grade of angiographic severity and considerable overlap between the groups (fig 4).

The pressure half times measured at catheterisation in the control group (mean (SD) 613 (157) ms, range 380–910 ms) were significantly different only from those of the patients with severe regurgitation ($p < 0.05$).

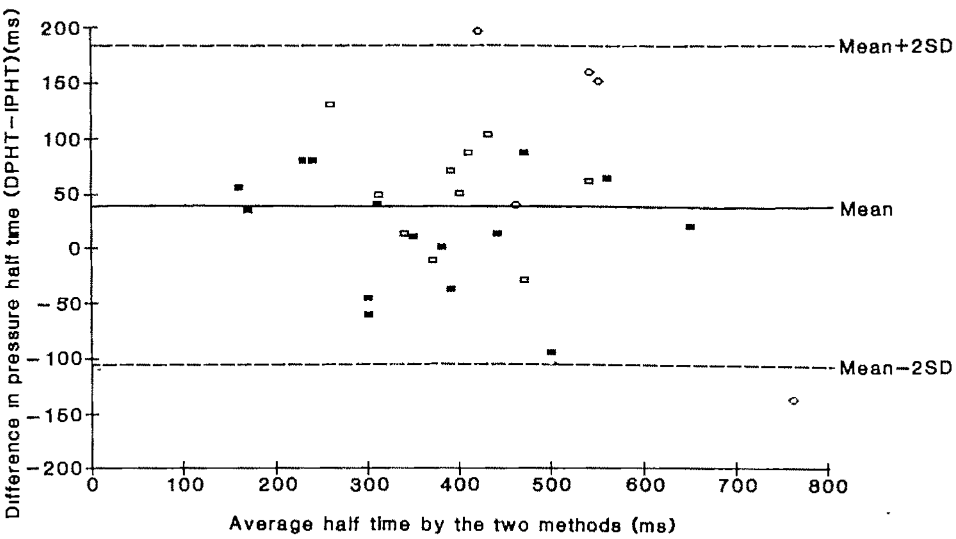


Fig 3 *Relation of the differences in pressure half time measured by the Doppler technique (DPHT) and by catheterisation (IPHT) to the mean pressure half time by both techniques. At angiography 15 patients were graded as having severe (■), 10 moderate (□), and 5 mild (◇) aortic regurgitation.*

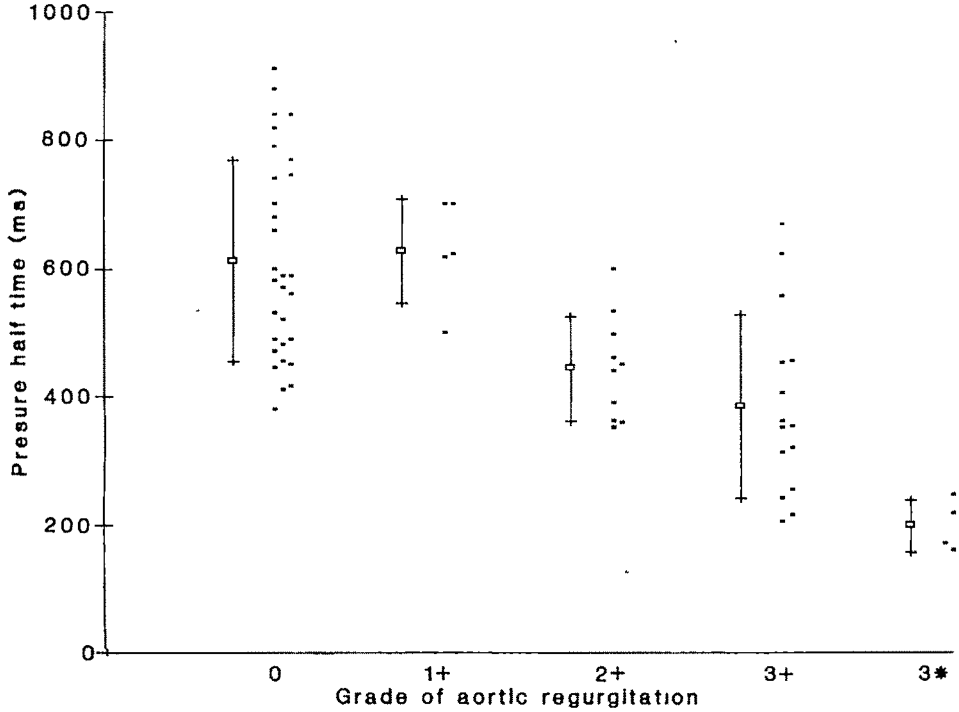


Fig 4 *Comparison between the pressure half time and the severity of aortic regurgitation assessed by angiography. In the control group (0) the half time was obtained from invasive measurements and in patients with aortic regurgitation from the non-invasive measurements (1+ – 3+). Angiographic assessment: 0 = no aortic regurgitation, 1+ = mild, 2+ = moderate, and 3+ = severe aortic regurgitation. Patients with severe aortic regurgitation at operation are shown as 3*. Mean (2SD) half times for each group are shown.*

PRESSURE HALF TIMES MEASURED NON-INVASIVELY AND SYSTEMIC VASCULAR RESISTANCE

There was a positive correlation between pressure half times measured by Doppler and systemic vascular resistance in patients with severe regurgitation ($r = 0{\cdot}65$, $p = 0{\cdot}012$, SEE 116 ms). There was no significant difference in systemic vascular resistance between the groups classified as having mild, moderate, or severe regurgitation at cineangiography.

The pressure half times as measured with Doppler did not correlate with heart rate, systolic or diastolic aortic pressure, or left ventricular end diastolic pressure. No significant difference in heart rate or systolic aortic pressure was found between the subgroups at catheterisation ($p > 0{\cdot}05$). Left ventricular end diastolic pressure was significantly higher in the patients with severe aortic regurgitation (mean (SD) 22·5 (8·8) mm Hg) than the patients with mild regurgitation (mean 16·4 (6·2) mm Hg) ($p < 0{\cdot}05$).

The patients showing the largest overlap in pressure half time between the groups with moderate and severe aortic regurgitation (patients 15, 16, and 17) had either severe regurgitation with high systemic vascular resistance (patients 16 and 17) or moderate regurgitation with low systemic vascular resistance (patient 15).

The four patients with severe aortic regurgitation who went to surgery without catheterisation had pressure half times measured by Doppler (mean 198 (40·2) ms, range 160–245 ms) that were significantly shorter than in the subgroups of patients with mild or moderate regurgitation at angiography ($p < 0{\cdot}05$).

Discussion

The results indicate that the half time of the aorto-ventricular pressure difference can be assessed non-invasively from the maximal velocity of aortic regurgitation estimated by continuous wave Doppler ultrasound if signals have a well defined maximal velocity envelope.

A comparison of the pressure half times in those with various angiographic grades of severity showed that neither the difference between means of moderate and severe nor that between means of mild and moderate regurgitation were significant. Only the mean of mild regurgitation differed significantly from the mean of severe regurgitation. In the four patients with severe regurgitation who went to operation without catheterisation, however, the pressure half times were significantly shorter than in the patients with mild or moderate regurgitation. Only in patients with severe regurgitation were pressure half times shorter than 300 ms recorded at catheterisation.

There may be several reasons for the wide range of pressure half times within each group and the overlap between the groups. Angiographic grading is a much less accurate estimate of the degree of regurgitation than the regurgitation fraction.[16 17] On the other hand, the pressure decrease in the aorta during diastole is dependent on the volume loss both to the left ventricle and to the systemic arteries. Provided that compliance and early diastolic pressure in the aorta are constant, a decrease in systemic vascular resistance would result in a faster volume transport to the body, and hence a more rapid decrease in aortic pressure. This would result in both a smaller volume loss to the left ventricle because of the reduced pressure and at the same time a faster pressure drop and a shortened pressure half time. We found a positive correlation between systemic vascular resistance and pressure half time ($p = 0{\cdot}012$) in patients in whom angiography showed severe regurgitation. However, because the patients included in this study were examined only once (without administration of drugs for provocation of changes in peripheral vascular resistance or for compliance measurements), the influence of systemic vascular resistance upon the pressure half time could not be evaluated further.

In patients with increased aortic compliance a larger volume variation may occur with less alteration in pressure, resulting in a longer pressure half time for the same volume change than in an aorta with normal or decreased compliance. With increased aortic compliance the pressure half time is influenced mainly by the left ventricular diastolic compliance.

For reliable measurements of the pressure half time of aortic regurgitation by continuous wave Doppler ultrasound a distinct envelope of the highest velocities from the regurgitation jet has to be obtained throughout diastole. The most common limitation in this study was insufficient delineation of the high velocities of the regurgitation jet. Because narrow jets give weaker signals than wide jets, patients with mild aortic regurgitation were less likely to be included in the study than patients with severe and moderate regurgitation.

The transducer needs to be positioned across the beginning of the jet to obtain a good envelope throughout diastole and a narrow angle between the regurgitation jet and the ultrasound beam gives a stronger signal than a wide angle. To obtain satisfactory recordings in some patients the transducer position was changed from the apical position to the parasternal or suprasternal positions. When the origin and direction of the regurgitation jet can be visualised by colour coded Doppler, later experience has indicated that a well defined envelope of the maximal jet velocities can be more rapidly obtained, and with a higher success rate also in patients with mild regurgitation.

The pressure half time is independent of the angle and not influenced by the blood pressure value, whereas the deceleration rate depends both on the initial pressure and the rate of pressure decrease. Others have measured the velocity half time or the deceleration of aortic regurgitations.[18 19] These measurements differ from the pressure half time by being influenced both by the angle between the ultrasound beam and jet velocity and by changes in blood pressure in early diastole.

The choice of different options for measuring the pressure half time described in the methods is more important in patients with less severe regurgitation where the velocity decay is curvilinear unless diastole is short. When the pressure half time was not reached before end diastole the linear decay in the first part of diastole was used because this measurement was independent of heart rate. This would, however, lead to relatively shorter half times in some of the patients with mild and moderate regurgitation and may partly account for the lack of a significant difference between moderate and severe regurgitation. However, values < 350 ms were not seen in patients with mild or moderate regurgitation.

In patients with severe regurgitation there was no difficulty with this measurement because they all showed a linear velocity decay, with a continued rapid decrease in velocity throughout diastole. Thus in addition to a shorter pressure half time in some of these patients, a continued rapid decrease in velocity instead of a curvilinear decay was a useful indicator of the severity. A rapid heart rate would make this difference in the velocity curves in late diastole less obvious.

Conclusions

In patients with aortic regurgitation the half time of the aortoventricular pressure difference can be measured non-invasively with Doppler ultrasound.

The wide scatter of pressure half times in the patients with mild or moderate regurgitation at cineangiography as well as in the control group suggests that other factors such as systemic vascular resistance and aortic and left ventricular compliance influence the pressure half time sufficiently to limit the usefulness of this measurement unless there is information on all variables. The method, however, is of value in detecting those patients with the most severe aortic regurgitation because the severity of the lesion and the need for early surgical intervention are not always recognised by clinical examination of these patients.

This study was supported by grants from the the Norwegian Council on Cardiovascular Diseases.

References

1 Quinones MA, Young JB, Waggoner AD, Ostojic MC, Ribeiro LGT, Miller RR. Assessment of pulsed Doppler echocardiography in detection and quantification of aortic and mitral regurgitation. *Br Heart J* 1980,**44**:612–20.

2 Wautrecht JC, Vandenbossche JL, Englert M. Sensitivity and specificity of pulsed Doppler echocardiography in detection of aortic and mitral regurgitation. *Eur Heart J* 1984;5:404–11.

3 Hatle L, Angelsen B Calculation of pressure drop. In: *Doppler ultrasound in cardiology*. 2nd ed. Philadelphia: Lea and Febiger, 1985:101–8.

4 Hatle L, Angelsen B. Aortic regurgitation. In: *Doppler ultrasound in cardiology*. 2nd ed. Philadelphia. Lea and Febiger, 1985.154–62.

5 Masuyama T, Kodama K, Kitabatake A, *et al.* Noninvasive evaluation of aortic regurgitation by continuous-wave Doppler echocardiography. *Circulation* 1986;73:460–6.

6 Teague SM, Heinsimer JA, Anderson JL, *et al.* Quantification of aortic regurgitation utilizing continuous wave Doppler ultrasound. *J Am Coll Cardiol* 1986,**8**:592–9.

7 Libanoff AJ. A hemodynamic measure of aortic regurgitation. Half-time of the rate of fall in aortic pressure during diastole. *Cardiology* 1973;**58**:162–73.

8 Judge TP, Kennedy JW. Estimation of aortic regurgitation by diastolic pulse wave analysis. *Circulation* 1970;**41**:659–65.

9 Hatle L, Angelsen B, Tromsdal A. Noninvasive assessment of atrioventricular pressure half-time by Doppler ultrasound. *Circulation* 1979;**60**:1096–104.

10 Bertrand ME, Widimsky J. Pressures. *Eur Heart J* 1985;**6**(suppl C):5–9.

11 Rokseth R, Helle I, Marstrander F, Storstein O. Reference level in pressure recordings during right heart catheterization. *Scand J Clin Lab Invest* 1960; **12**.116–20.

12 Yang SS, Bentivoglio LG, Maranhao V, Goldberg H. *From cardiac catheterization data to hemodynamic parameters.* 2nd ed. Philadelphia: FA Davies, 1978:56–62.

13 Eie H. Cineangiocardiography in cardiac valvular disease. *Tidsskr Nor Laegeforen* 1971;**91**:647–53.

14 Glantz SA. *Primer of biostatistics*. 2nd ed. New York: McGraw-Hill, 1987:64–100.

15 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement *Lancet* 1986;**i**:307–10.

16 Hunt D, Baxley WA, Kennedy JW, Judge TP, Williams JE, Dodge HT. Quantitative evaluation of cineaortography in the assessment of aortic regurgitation. *Am J Cardiol* 1973;**31**:696–700.

17 Croft CH, Lipscomb K, Mathis K, *et al.* Limitations of qualitative angiographic grading in aortic or mitral regurgitation. *Am J Cardiol* 1984;**53**:1593–8.

18 Labotvitz AJ, Ferrara RP, Kern MJ, Bryg RJ, Mrosek DG, Williams GA. Quantitative evaluation of aortic insufficiency by continuous wave Doppler echocardiography. *J Am Coll Cardiol* 1986,**8**:1341–7.

19 Beyer RW, Ramirez M, Josephson MA, Shah PM. Correlation of continuous-wave Doppler assessment of chronic aortic regurgitation with hemodynamics and angiography. *Am J Cardiol* 1987,**60**:852–6

Br Heart J 1989;61:344–7

Transmitral velocities measured by pulsed Doppler in healthy volunteers: effects of acute changes in blood pressure and heart rate

S A SMITH, J E STONER, A E RUSSELL, J M SHEPPARD, P E AYLWARD

From the Department of Medicine, Flinders Medical Centre, Bedford Park, South Australia

SUMMARY The effect of a two minute cold pressor test on transmitral velocities measured by pulsed Doppler was studied in 11 healthy volunteers. Blood pressure increased significantly during cold immersion but peak atrial and peak early diastolic transmitral velocities and their ratio (A:E) were unchanged. There was no correlation between changes in Doppler variables and changes in calculated mean arterial blood pressure during the test. Heart rate changes were variable and not related to changes in blood pressure. In individual people the change in pulse interval during cold immersion was significantly and inversely correlated with the change in the A:E ratio.

The large acute increase in arterial pressure seen during the cold pressor test in normal volunteers had no consistent effect on the transmitral velocity profile although small changes in heart rate were associated with large changes in A:E ratio. The effect of small changes in heart rate may be of considerable importance in determining transmitral velocity profiles. Thus in clinical and experimental studies in which the heart rate is not controlled, Doppler data on transmitral flow should be interpreted with caution.

Alterations in transmitral velocities measured by Doppler, particularly the ratio of peak atrial to peak early diastolic flow (A:E ratio), have been attributed to abnormal left ventricular relaxation.[1 2] Pulsed Doppler echocardiography has been widely used to examine left ventricular diastolic function in people with hypertension,[3] hypertrophic cardiomyopathy,[4] and ischaemic heart disease.[5]

Recently it has been recognised that factors other than myocardial disease, including age,[6 7] left ventricular preload,[8] end diastolic pressure,[9] and Doppler sample site[10] may alter transmitral flow measurements.

Two studies of invasive measurements of haemodynamic variables in dogs suggested that the rate of left ventricular relaxation may be partly determined by left ventricular afterload.[11 12] There are no data on the effect of acute changes in afterload on transmitral velocity measured by Doppler in healthy people.

We examined the effect of a standard cold pressor test, which produces large changes in blood pressure, and thus afterload,[13] on transmitral velocity in healthy volunteers.

Patients and methods

We studied 11 untreated, healthy volunteers (eight men, three women, mean (SD) age of 34·4 (5·9) years, range 24 to 44 years). They had no history of hypertension, cardiovascular disease, or excessive alcohol consumption.

PROTOCOL

All measurements were made in a quiet laboratory with a constant ambient temperature of 21°C. Volunteers were positioned in a left lateral semirecumbent position and this was adjusted until optimal Doppler recordings were obtained: thereafter the volunteers' position was not changed. After they had rested for 10 minutes they immersed their right hands in melting ice for two minutes. Blood pressure was recorded indirectly with a standard mercury sphygmomanometer and heart rate was measured from the electrocardiogram. The mean blood pres-

Requests for reprints to: Dr P E Aylward, Department of Medicine, Flinders Medical Centre, Bedford Park, South Australia 5042, Australia.

Accepted for publication 8 December 1988

sure was calculated as diastolic pressure plus one third of the pulse pressure.

DOPPLER RECORDING AND ANALYSIS

Pulsed Doppler examinations of transmitral flow were recorded continuously on videotape throughout the cold pressor test on a Diasonics CV 400 ultrasound system with a transducer emission frequency of 3 0 MHz. The Doppler sample volume was placed, without angle correction, in the mitral valve funnel just to the left ventricular side of the mitral annulus and with the ultrasound beam as parallel as possible to left ventricular inflow.

We analysed the Doppler profiles recorded immediately before the cold pressor test, at one and two minutes during the test, and one minute after the test. Peak early diastolic velocity (E), peak atrial velocity (A), their ratio (A:E), and the corresponding pulse intervals (RR) were averaged over five consecutive cardiac cycles.

Data were expressed as mean (SD). Formal tests of statistical significance were obtained by standard methods of analysis of variance and linear regression analysis. Statistical significance is reported for p values of < 0·05.

Table 1 *Peak atrial (A) and early (E) diastolic velocities, their ratio (A:E), pulse interval (RR), and mean blood pressure (MBP) measured before, after one and two minutes of a cold pressor test, and one minute after the end of the test*

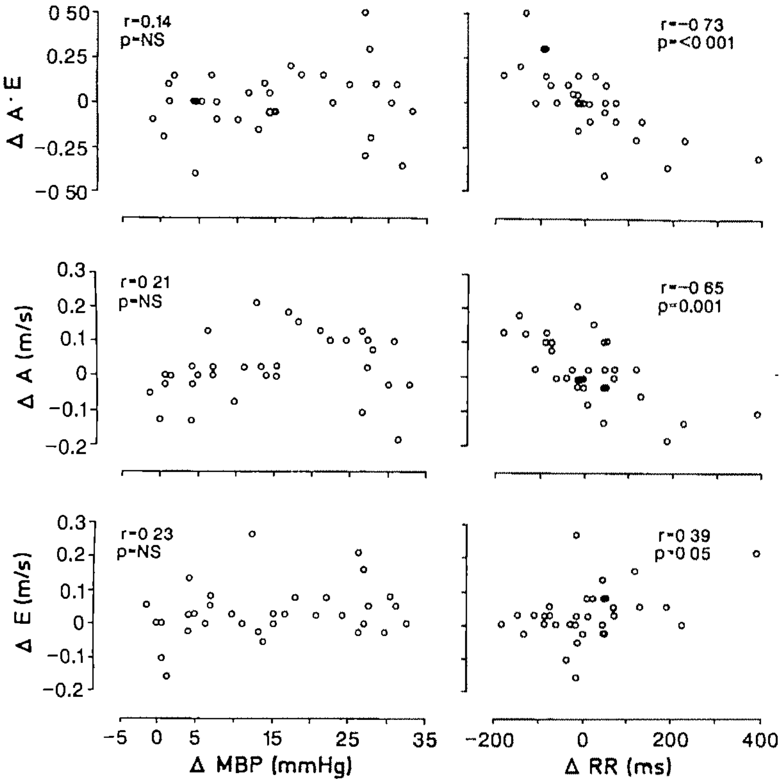
	A *(m/s)*	*E* *(m/s)*	*A.E*	*RR* *(ms)*	*MBP* *(mm Hg)*
Before	0 42 (0 02)	0 62 (0 04)	0 72 (0 08)	872 (48)	81 (2)
1 min	0 46 (0 03)	0 62 (0 04)	0·79 (0 10)	857 (46)	101 (3)*
2 min	0·45 (0 03)	0 66 (0 04)	0 79 (0 11)	901 (52)	102 (3)*
After	0·42 (0 04)	0 66 (0 03)	0 65 (0 08)	899 (32)	86 (3)

*p < 0 001 compared with values before test

Results

HAEMODYNAMIC EFFECTS OF THE COLD PRESSOR TEST

Mean arterial blood pressure increased by approximately 20 mm Hg (p < 0·001) during the cold pressor test (table) and returned to pretest values within one minute of the removal of the hand from the ice. Heart rate did not change significantly during the cold pressor test and we found no relation between changes in heart rate and blood pressure.



Relations between individual changes from baseline of mean blood pressure (MBP) and pulse interval (RR) and individual changes in peak early (E) and atrial (A) diastolic transmitral velocities and their ratio (A:E) during (1 and 2 minutes) and after (1 minute) the cold pressor test in eleven healthy individuals.

DOPPLER VARIABLES AND THEIR RELATION TO BLOOD PRESSURE

There were no significant changes in peak atrial velocity (A), peak early diastolic velocity (E), or A:E ratio at any stage of the cold pressor test despite a 20 mm Hg increase in mean arterial pressure. The changes in mean arterial blood pressure within individuals did not correlate with changes in A, E, or A:E (figure).

DOPPLER VARIABLES AND THEIR RELATION TO HEART RATE

Though heart rate did not change during or after the cold pressor test in the group as a whole, the heart rate increased in some individuals and decreased in others. Changes in A:E within each individual correlated significantly with the change in RR (figure). This correlation was mainly the result of an inverse relation between changes in RR and in peak atrial velocity (A), though a less striking, but still statistically significant, positive correlation was noted between changes in RR and in peak early diastolic velocity.

Discussion

This study shows that transmitral velocity measured by Doppler is not affected by large changes in arterial pressure but it is considerably affected by small changes in heart rate.

The cold pressor test reliably increases blood pressure with small or inconsistent effects on other relevant haemodynamic variables.[13] We used the cold pressor test to assess the effects of acute changes in blood pressure on transmitral velocities measured by Doppler. Analysis of transmitral flow by Doppler has been advocated as a method for examining left ventricular diastolic function[1 2] and animal experiments have suggested that the rate of left ventricular relaxation may be partly determined by afterload.[11 12] The original purpose of this study was to examine the effects of changes in blood pressure on Doppler variables in order to determine whether such changes need to be taken into account when serial Doppler examinations are interpreted.

Because we were unable directly to measure changes in central haemodynamic variables in this non-invasive study we cannot exclude changes in preload in our study group, but earlier work suggests that changes in preload are likely to be small.[13] Because the experiment was performed in conscious people, a direct effect of increased afterload on left ventricular relaxation (and thus Doppler transmitral velocity) may have been opposed by reflex effects. Whatever the mechanism, we found no consistent relation between large acute changes in blood pressure and changes in Doppler variables, suggesting that changes in afterload can be ignored in an interpretation of Doppler measures of mitral flow. Our data do not exclude the possibility of a small effect of blood pressure variation on Doppler variables, but any such effect would be of little importance in practice. Further studies are required before conclusions can be drawn about the effects of acute changes in blood pressure in patients with cardiovascular disease.

We found that the peak velocity of the atrial component of diastolic flow was inversely related to the pulse interval within individuals. Our data suggest that a small change in heart rate from 70 to 80 beats/min would increase the ratio of peak atrial to peak early diastolic transmitral velocity (A:E) by approximately 30%. Other studies that have specifically examined the effects of changes in heart rate on transmitral velocities measured by Doppler have shown similarly pronounced effects of heart rate. Gillam *et al* using programmed pacing showed a tenfold change in E:A ratio as heart rate was changed from 60 to 100 beats/min.[14] Parker *et al* using atropine showed a similar dependency of A:E on heart rate.[15] This relation between changes in heart rate and in peak atrial velocity and A:E ratio may be of considerable clinical and experimental importance. Reliable correction for changes in heart rate between sequential studies will not be possible until the precise relation between heart rate and transmitral flow is fully established. There are many published reports of changes in A:E after procedures such as coronary angioplasty,[16 17] head up tilting,[18] and administration of vasoactive drugs.[8 19] The results of such studies may not be valid if the heart rate changed between the Doppler examinations.

Serial measurements of transmitral velocity profiles are not significantly affected by large changes in blood pressure in healthy volunteers. In clinical and experimental studies in which the heart rate changes, Doppler data on transmitral velocity should be interpreted with caution.

SAS was a British Heart Foundation/Australian National Heart Foundation reciprocal travelling fellow. AER holds a Lions Postgraduate Medical Research Scholarship. We thank Mrs S Taylor for her assistance with analysis of the data and the illustrations.

References

1 Snider AR. Prediction of intracardiac pressures and assessment of ventricular function with Doppler echocardiography. *Echocardiography* 1987;4:305–20.
2 DeMaria AN, Wisenbaugh T. Identification and treatment of diastolic dysfunction: role of transmitral

Doppler recordings. *J Am Coll Cardiol* 1987;**9**: 1106–7

3 Snider AR, Gidding SS, Rocchini AP, *et al.* Doppler evaluation of left ventricular diastolic filling in children with systemic hypertension. *Am J Cardiol* 1985;**56**:921–6.

4 Maron BJ, Spirito P, Green KJ, Wesley YE, Bonow RO, Arce J. Noninvasive assessment of left ventricular diastolic function by pulsed Doppler echocardiography in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1987;**10**:733–42.

5 Harrison MR, Smith MD, Friedman BJ, DeMaria AN. Uses and limitations of exercise Doppler echocardiography in the diagnosis of ischaemic heart disease. *J Am Coll Cardiol* 1987;**10**:809–17.

6 Miller TR, Grossman SJ, Schectman KB, Biello DR, Ludbrook PA, Ehsani AA. Left ventricular diastolic filling and its association with age. *Am J Cardiol* 1986;**58**:531–5.

7 Kuo LC, Quinones MA, Rokey R, Sartori M, Abinader EG, Zoghbi WA. Quantification of atrial contribution to left ventricular filling by pulsed Doppler echocardiography and the effect of age in normal and diseased hearts. *J Am Cardiol* 1987;**59**:1174–8.

8 Choong CY, Herrmann HC, Weyman AE, Fifer MA. Preload dependence of Doppler derived indices of left ventricular diastolic function in humans. *J Am Coll Cardiol* 1987;**10**:800–8.

9 Channer KS, Culling W, Wilde P, Jones JV. Estimation of left ventricular end diastolic pressure by pulsed Doppler ultrasound. *Lancet* 1986;**i**:1005–7.

10 Gardin JM, Dabestani A, Takenaka K, *et al.* Effect of imaging view and sample volume location on evaluation of mitral flow velocity by pulsed Doppler echocardiography. *Am J Cardiol* 1986;**57**:1135–9.

11 Gaash WH, Blaustein AS, Andrias CW, Donahue RP, Avitall B. Myocardial relaxation. II. Hemodynamic determinants of rate of left ventricular isovolumic pressure decline. *Am J Physiol* 1980;**239**:H1–6.

12 Karliner JS, LeWinter MM, Mahler F, Engler R, O'Rourke RA. Pharmacologic and hemodynamic influences on the rate of isovolumic left ventricular relaxation in the normal conscious dog. *J Clin Invest* 1977;**60**:511–22.

13 Greene MA, Boltax AJ, Lustig GA, Rogow E. Circulatory dynamics during the cold pressor test. *Am J Cardiol* 1965;**16**:54–60

14 Gillam DL, Shunichi H, Novick SS, Rediker DE, Eagle KA. The influence of heart rate Doppler mitral flow patterns [Abstract]. *Circulation* 1987;**76**(suppl IV): IV–123.

15 Parker TG, Cameron D, Serra J, Morgan CD, Sasson Z. The effect of heart rate and A–V interval on Doppler ultrasound indices of LV diastolic function [Abstract]. *Circulation* 1987;**76**(suppl IV):IV–124.

16 Wind BE, Snider AR, Buda AJ, O'Neill WW, Topol EJ, Dilworth LR. Pulsed Doppler assessment of left ventricular diastolic filling in coronary artery disease before and immediately after coronary angioplasty. *Am J Cardiol* 1987;**59**:1041–6.

17 Labovitz AJ, Lewen MK, Kern M, *et al.* Evaluation of left ventricular systolic and diastolic dysfunction during transient myocardial ischaemia produced by angioplasty. *J Am Coll Cardiol* 1987;**10**:748–55.

18 Leeman DE, Feldman MD, Diver DJ, Santinga JT, Come PC Effects of decreases in preload on pulsed Doppler indices of left ventricular filling [Abstract]. *Circulation* 1986;**74**(suppl II):II–46.

19 Iwase M. Sotobata I, Takagi S, Miyaguchi K, Jing HX, Yokota M. Effects of diltiazem on left ventricular diastolic behaviour in patients with hypertrophic cardiomyopathy: evaluation with exercise pulsed Doppler echocardiography. *J Am Coll Cardiol* 1978;**9**:1099–105.

Br Heart J 1989;61:348–55

Isoprenaline as an aid to the induction of catecholamine dependent supraventricular tachycardias during programmed stimulation

BÉATRICE BREMBILLA-PERROT, A TERRIER DE LA CHAISE, MARC PICHENÉ, ETIENNE ALIOT, FRANÇOIS CHERRIER, CLAUDE PERNOT

From the Department of Cardiology, Brabois Hospital, Vandoeuvre lès Nancy, France

SUMMARY The effects of isoprenaline on the induction of supraventricular tachycardia by programmed stimulation were studied in 67 patients to see whether they correlated with spontaneous catecholamine mediated symptoms during exercise testing and Holter monitoring. Thirty seven control patients (group 1) did not have spontaneous arrhythmias either during exercise testing or Holter monitoring. Thirty patients (group 2) had documented exercise or stress related supraventricular tachycardias—that is paroxysmal junctional tachycardia (24) or atrial arrhythmia (6). Programmed electrical stimulation was performed before and during the infusion of isoprenaline. No group 1 patient developed sustained supraventricular tachycardia during isoprenaline infusion. In 21 patients with paroxysmal junctional tachycardia and all the patients with atrial arrhythmias electrical stimulation during isoprenaline infusion produced the same tachycardia that had been seen during exercise testing and Holter monitoring. Changes in electrophysiological variables and the concentrations of serum potassium were not associated with the induction of supraventricular tachycardia by isoprenaline. Infusion of isoprenaline safely facilitated the induction of supraventricular tachycardia by programmed stimulation in patients who had spontaneously occurring catecholamine mediated symptoms.

Although isoprenaline is known to facilitate the induction of ventricular tachycardia[1 2] it has rarely been used to aid the electrical induction of supraventricular tachycardia.

We report the results obtained when small infusions of isoprenaline were given to patients who did not have clinical supraventricular tachycardia and in whom standard stimulation techniques failed to induce tachycardia and to patients who did have spontaneous but non-inducible tachycardia.

Patients and methods

PATIENTS

Sixty seven patients who underwent programmed stimulation of the heart were classified according to the presence or absence of clinical and inducible supraventricular tachycardias.

Group 1

Group 1 consisted of 37 patients aged from 12 to 67 (average 45) who had no clinical history of tachycardia. Seventeen had underlying heart disease: dilated cardiomyopathy (three), hypertrophic cardiomyopathy (five), coronary heart disease (two), mitral valve prolapse (two), congenital heart disease (four), valve disease (one). Four patients in group 1 had Wolff-Parkinson-White syndrome. Electrophysiological studies were performed to investigate the cause of syncope (12) or dizziness (17). These studies, which included ventricular stimulation, were also completed in eight patients with underlying heart disease (four cases) or were performed to assess the severity of Wolff-Parkinson-White syndrome (four cases). Twenty four hour Holter monitoring showed no evidence of supraventricular arrhythmias (three patients had atrial extrasystoles). No tachycardia or atrial extrasystoles were seen during upright bicycle exercise testing at an initial workload of 25 W, with subsequent increases of 25 W every two minutes. Exercise continued until exhaustion or the onset of symptoms.

Requests for reprints to Dr Béatrice Brembilla-Perrot, Department of Cardiologie, CHU de Brabois, 54500 Vandoeuvre les Nancy, France

Accepted for publication 1 November 1988

No supraventricular tachycardia was induced by programmed stimulation in the basal state.

Group 2

Group 2 consisted of 30 patients aged from 15 to 80 (average 45) who had been admitted with supraventricular tachycardias and who had been included in a group of about 160 patients with supraventricular tachycardia studied in the laboratory over four years (1983 to 1987). Group 2a consisted of 24 patients with paroxysmal regular junctional reciprocating tachycardia and group 2b consisted of six patients with paroxysmal atrial arrhythmias—atrial fibrillation (two), atrial flutter (one), and atrial tachycardia (three). All the patients in group 2 had tachycardia induced by exercise or psychological stress. In most an electrocardiographic recording of the tachycardia was available. None the less, only eight of the 29 patients who exercised on the bicycle showed supraventricular arrhythmias during exercise. There were frequent salvoes of atrial extrasystoles (five), atrial tachycardia (one), and paroxysmal junctional tachycardia (two) immediately after exercise. Twenty four hour Holter monitoring in all the patients showed a paroxysmal junctional tachycardia in nine patients and atrial tachycardia in three patients. Nine patients had underlying heart disease: mitral valve prolapse (six), valvar heart disease (one), and dilated cardiomyopathy (two). Eight patients had Wolff-Parkinson-White syndrome. Electrophysiological study was performed to investigate the mechanism of the tachycardia (23) or syncope associated with tachycardia (seven).

All patients had normal serum concentrations of potassium. Cardioactive drugs were stopped at least five half lives before the study.

ELECTROPHYSIOLOGICAL STUDIES

Electrophysiological studies were performed in non-sedated patients in the post-absorptive state after they had given their informed consent. All patients were in normal sinus rhythm at the time of study. Right heart catheterisation was performed through the femoral vein with three 6 or 7 French multi-electrode catheters. Electrograms were recorded from the right atrium, the atrioventricular (AV) junction (His bundle electrogram), and the coronary sinus. Atrial and ventricular stimulation was performed with a programmable digital stimulator (Explorer 2000 Ela Médical) that delivered rectangular pulses lasting 1 8 ms at twice the diastolic threshold. Intracardiac electrograms and electrocardiographic leads I, III, and VI were simultaneously displayed on a multichannel oscilloscope (Siemens recording system) and recorded at a paper speed of 25 to 100 mm/s. Arterial blood pressure was measured by sphygmomanometry every five minutes.

We used the following protocol of programmed stimulation: (*a*) incremental atrial pacing up to the onset of type 1 second degree block; (*b*) atrial extrastimulus testing during sinus rhythm (S2) and atrial pacing at cycle lengths of 600 and 400 ms (S1 S2); (*c*) incremental ventricular pacing up to the onset of retrograde ventriculoatrial (VA) second degree or higher grades of ventriculoatrial block (maximal pacing rate 220 beats/min); (*d*) ventricular extrastimulus techniques up to S3 during sinus rhythm and ventricular pacing (cycle lengths of 600 and 400 ms) with two stimuli. In 21 patients the plasma concentration of potassium was measured after programmed stimulation in 21 patients.

Isoprenaline infusion was started at 0·5 μg/min and adjusted to increase the basal heart rate by at least 20%. In all patients the heart rate was increased to at least 100 beats/min (maximum of 150 beats/min). During the infusion we repeated the stimulation protocol and measured the serum concentration of potassium at comparable cycle lengths. The effective refractory periods were determined at a cycle length of 400 ms. The amount of isoprenaline required to induce the desired changes in heart rate ranged from 6 to 20 μg.

Heart rate and blood pressure were monitored continuously throughout the study.

DEFINITION OF TERMS

Non-sustained supraventricular tachycardia: at least five consecutive atrial extrasystoles, but less than one minute of tachycardia reproducibly induced.

Sustained supraventricular tachycardia: tachycardia that lasted more than one minute.

Non-sustained ventricular tachycardia: at least five consecutive ventricular extrasystoles, but reproducibly induced for less than one minute.

Sustained ventricular tachycardia: tachycardia that lasted more than one minute.

STATISTICAL ANALYSIS

We used a two tailed *t* test for independent or paired samples. Numerical data are presented as mean (1 SD).

Results

Tables 1–3 show the results of electrophysiological testing in all the study groups.

ELECTROPHYSIOLOGICAL VARIABLES (TABLE 4)

The effects of isoprenaline on heart rate and the AH and HV intervals were similar to those previously reported.[3] Isoprenaline shortened the length of the sinus cycle in group 1 and in group 2. It also

Table 1 *Results of electrophysiological study before and after infusion of isoprenaline (Iso)*

Case	Sex	Age (yr)	Indic	ECG	HD	ET	Holter	CL (ms)	AH (ms)	Ant 2nd° block (beats/min)	Retr block (beats/min)	A Stim	K+ (mmol/l)
1	M	60	S	N	HCM	—	—	850	120	100	0	—	
								Iso 500	60	160	200	—	
2	M	48	S	N	—	—	—	1000	70	160	0	—	
								Iso 470	50	190	200	—	
3	F	66	S	N	—	—	—	650	50	170	160	—	
								Iso 500	50	230	200	AESs	
4	M	67	S	SB	—	—	—	1300	75	120	90	—	
								Iso 650	70	190	100	—	
5	M	62	S	MA	CHD	—	—	750	70	205	0	—	
								Iso 550	60	230	0	—	
6	F	63	D	N	Valv	—	—	620	70	220	0	—	
								Iso 480	60	300	200	—	
7	M	51	D	SB	—	—	—	1100	80	100	100	E	3·9
								Iso 600	60	210	230	E	3·5
8	M	66	S	LBBB	—	—	—	780	70	160	160	—	4·3
								Iso 650	70	260	220	—	4·1
9	M	30	D	N	—	—	—	650	50	230	0	—	
								Iso 450	40	320	240	E	
10	M	37	D	N	—	VESs	VESs	550	60	240	210	NSAF	3·5
								Iso 400	30	290	220	—	3·4
11	F	62	D	N	HCM	—	—	1140	90	150	130	—	3·9
								Iso 600	80	230	220	—	3·9
12	M	46	S	N	—	—	—	920	100	170	110	E	3·8
								Iso 750	70	250	180	—	3·1
13	M	49	D	N	HCM	VESs	VESs	1000	40	210	130	E	4·3
								Iso 440	65	260	220	—	3·6
14	F	40	S	N	—	—	VESs	800	75	160	0	—	
								Iso 500	70	240	180	—	
15	M	35	S	N	—	VESs	VESs	800	100	140	0	NSAF	
								Iso 400	70	210	0	—	
16	F	64	D	N	—	—	VESs	1050	60	170	140	—	
								Iso 700	J	200	190	—	
17	F	36	D	N	RVD	—	VESs	650	50	240	0	E	
								Iso 450	40	300	200	—	
18	M	51	D	MI	CHD	—	—	870	80	170	170	—	
								Iso 550	60	250	200	—	
19	F	12	syst	RVH	cong	VESs	—	750	110	170	0	—	
								Iso 400	90	300	0	—	
20	M	61	syst	RBBB	HCH	—	VESs	650	75	190	110	—	
								Iso 550	75	250	220	—	
21	M	30	D	N	DCM	—	—	850	100	150	0	—	4·9
								Iso 500	60	230	0	—	3·7
22	M	56	S	N	—	—	VESs	660	100	150	0	—	
								Iso 500	60	230	0	—	
23	M	42	syst	LVH	DCM	—	VESs	600	40	200	170	—	3·6
								Iso 540	80	270	200	—	3·3
24	F	50	D	N	—	—	VESs	700	75	210	0	—	4·1
								Iso 450	60	230	220	—	3·7
25	F	16	D	N	RVD	VESs	VESs	750	100	150	0	NSAF	3·8
								Iso 380	80	280	240	—	3
26	M	56	D	N	—	—	—	850	120	100	0	—	
								Iso 500	60	160	200	—	
27	F	56	D	N	—	—	—	750	70	160	190	E	
								Iso 500	60	200	200	—	
28	M	17	S	N	MVP	—	VESs	950	90	150	100	—	
								Iso 500	70	210	150	—	
29	F	59	D	N	RVD	VESs	VESs	750	90	190	0	—	
								Iso 400	70	220	0	—	
30	M	46	S	LVH	HCM	—	—	950	95	170	0	—	
								Iso 510	65	220	120	—	
31	M	51	syst	LVH	DCM	—	—	620	80	180	190	—	3·7
								Iso 500	65	210	220	—	2·9
32	M	37	D	N	MVP	—	VESs	850	75	180	130	NSAF	4·6
								Iso 500	60	260	190	—	3·8
33	M	2	S	N	HCM	—	—	1050	70	110	0	NSAF	6·1
								Iso 550	55	250	190	—	4·6
34	M	37	syst	WPW	—	—	VESs	750	70	190	190	—	
								Iso 400	60	280	280	—	
35	F	25	syst	WPW	—	—	—	750	80	180	180	E	
								Iso 350	50	300	300	E	
36	M	35	syst	WPW	—	—	—	800	50	250	250	—	
								Iso 600	50	280	280	—	
37	M	14	syst	WPW	—	—	—	520	75	220	220	—	
								Iso 400	50	280	280	NSAF	

Indic (indication)—S, syncope; D, dizziness, syst, systematically (to study tachycardia induction).
ECG (electrocardiogram)—N, normal, SB, sinus bradycardia, MI, myocardial infarction, LBBB, left bundle branch block, LVH, left ventricular hypertrophy; RBBB, right bundle branch block, RVH, right ventricular hypertrophy.
HD (heart disease)—HCM, hypertrophic cardiomyopathy; CHD, coronary heart disease, RVD, right ventricular dysplasia, cong, congenital HD, DCM, dilated cardiomyopathy; MVP, mitral valve prolapse.
ET (exercise testing)—VES, ventricular extrasystole
CL, cycle length, Ant 2nd° block, heart rate at which atrioventricular second degree block occurred; Retr block, heart rate at which ventriculoatrial block occurred; A Stim, results of programmed atrial stimulation, AES, atrial extrasystole; E, repetitive atrial echo beat, NSAF, non-sustained atrial fibrillation

Table 2 *Patients with exercise related paroxysmal junctional tachycardias (group 2a)*

Case	*Sex*	*Age (yr)*	*Indic*	*ECG*	*HD*	*ET*	*Holter*	*CL (ms)*	*AH (ms)*	*Ant 2nd° block (beats/min)*	*Retr block (beats/min)*	*A Stim*	*K+ (mmol/l)*
1	F	24	T	WPW	MVP	—	—	100	100	120	200	E	
								Iso 500	80	240	200	SPJT	
2	F	59	T	WPW	—	—	—	900	90	140	190	—	
								Iso 450	60	250	200	SPJT	
3	M	28	T	N	—	—	—	800	90	160	0	—	
								Iso 450	60	260	200	—	
4	M	55	T	N	—	—	—	900	70	185	150	—	
								Iso 500	60	210	200	SPJT	
5	M	31	T-S	N	—	—	—	870	90	180	140	NSAT	
								Iso 450	70	250	200	SPJT	
6	M	57	T	WPW	MVP	—	PJT	1000	70	150	200	NSPJT	
								Iso 450	60	250	200	SPJT	
7	F	33	T-S	WPW	—	—	—	750	60	150	180	E	
								Iso 350	45	300	200	NSPJT	
8	F	33	T	WPW	—	—	—	1000	130	120	160	NSPJT	
								Iso 500	70	230	200	SPJT	
9	F	60	T-S	WPW	—	—	—	700	80	180	160	NSAFI	
								Iso 450	50	240	200	SPJT	
[illegible]0	M	34	T	RBBB	MVP	—	PJT	960	90	150	0	—	
								Iso 500	70	250	170	SPJT	
11	F	80	T-S	N	—	?	PJT	600	90	170	0	NSAT	
								Iso 500	80	190	160	SPJT	
2	M	15	T	N	—	—	—	860	70	145	170	—	
								Iso 500	50	210	200	SPJT	
3	F	61	T	N	MVP	—	PJT	1000	130	135	170	NSPJT	
								Iso 700	70	230	200	SPJT	
4	M	33	T	N	—	—	—	770	75	215	180	NSPJT	
								Iso 550	60	240	240	SPJT	
5	M	29	T	WPW	—	PJT	PJT	800	60	160	210	—	
					—	(post ET)		Iso 420	40	230	210	—	
6	F	31	T	N	—	—	—	660	110	170	120	O	
								Iso 500	60	270	220	SPJT	
7	M	26	T	N	—	—	—	800	80	150	180	E	4 2
								Iso 420	50	250	240	SPJT	2 7
8	M	46	T	LVH	DCM	AESs	PJT	640	90	220	200	—	4
								Iso 420	70	240	200	SPJT	3 5
9	M	52	T	LVH	DCM	—	VESs	800	70	150	150	NSA fl	4 5
								550	60	210	220	SPJT	3 5
[illegible]0	M	64	T-S	N	—	AESs	AT	750	60	230	180	E	3 4
								Iso 450	45	310	230	SPJT	3 5
1	F	45	T	N	—	—	PJT	710	75	220	150	NSAF	3 5
							VT	Iso 400	35	280	240	SPJT	3 3
2	F	33	T-D	WPW	—	PJT	PJT	800	45	210	130	NSAF	3 5
						(post ET)		Iso 430	40	290	220	SPJT	3 3
3	F	61	T	N	MVP	—	NS PJT	1000	140	140	0	NSAFI	4 1
							VESs	Iso 570	90	210	160	SPJT	2 7
4	F	43	T	N	—	—	—	720	60	200	170	NSPJT	3 4
								Iso 500	60	300	> 240	SPJT	3 4

PW, Wolff-Parkinson-White, AT, atrial tachycardia, PJT, paroxysmal junctional tachycardia, S, sustained, NS, non-sustained, AF, atrial fibrillation, A fl, ial flutter See footnote to table 1 for other abbreviations

able 3 *Results of electrophysiological study before and after infusion of isoprenaline in patients with exercise related paroxysmal atrial rhythmias (group 2b)*

se	*Sex*	*Age (yr)*	*Indic*	*ECG*	*HD*	*ET*	*Holter*	*CL (ms)*	*AH (ms)*	*Ant 2nd° block (beats/min)*	*Retr block (beats/min)*	*A Stim*	*K+ (mmol/l)*
	F	49	T	N	MVP	—	—	900	70	140	0	E	
								Iso 500	60	—	160	SAfl	
	M	50	T	N	—	AESs	—	700	90	210	150	—	
								Iso 600	80	240	200	SAF	
	F	56	T-S	LVH	Valve	AESs	—	800	80	130	110	NSAF	
								Iso 500	60	230	200	SAF	
	M	61	T	N	—	AT	—	1000	120	105	0	—	
								Iso 480	120	2nd° AVB	0	SAT	
	M	66	T	N	DCM	AESs	AT	770	60	160	110	NSAT	3 5
								Iso 640	60	280	220	SAT	3 5
	M	47	T	1st° AVB	—	AESs	AT	1100	130	90	90	NSAT	
								Iso 800	70	170	?	SAT	

B, atrioventricular block See footnotes to tables 1 and 2 for other abbreviations.

Table 4 *Electrophysiological variables (mean (1SD) before and after isoprenaline (Iso)*

	CL (ms)	*AH (ms)*	*Ant 2nd° block (beats/min)*	*Retr block (beats/min)*	*K^+ (mmol/l)*
Group 1.					
Before	812 (75)	82 (21)	173 (39)	104 (51)	4·2 (0·7)
Iso	505 (91)	62 (13)	243 (40)	177 (64)	3·6 (0·7)
p	< 0·001	< 0·001	< 0·001	< 0·001	< 0·03
Group 2:					
Before	832 (123)	86 (23)	169 (32)	143 (52)	3·9 (0·4)
Iso	485 (70)	63 (18)	245 (31)	204 (37)	3·3 (0·4)
p	< 0·001	< 0·001	< 0·001	< 0·001	< 0·01

shortened the AH interval in group 1 and in group 2 and had no effect on the HV interval. Isoprenaline reduced the atrial effective refractory period calculated at a driven atrial rhythm of 400 ms in both group 1 (218 (12) ms *v* 171 (14) ms, $p < 0{\cdot}01$) and group 2 (209 (16) ms *v* 165 (19) ms, $p < 0{\cdot}01$). The atrial rate at which anterograde type 1 second degree block developed increased significantly in group 1 and group 2. The ventricular rate at which retrograde second degree block developed increased significantly in group 1 and group 2. Isoprenaline reduced the ventricular effective refractory periods calculated at a driven rhythm of 400 ms from 210 (5) ms to 175 (7) ms ($p < 0{\cdot}01$) in group 2 and from 202 (7) ms to 173 (5) ms ($p < 0{\cdot}01$) in group 2. The effects of isoprenaline on the anterograde and retrograde refractory periods of Kent bundles were similar to those reported elsewhere[4]: isoprenaline generally shortened the refractory periods in patients with the longest initial values (average 50 ms).

SERUM CONCENTRATIONS OF POTASSIUM

The serum concentration of potassium fell significantly in group 1.

INDUCED SUPRAVENTRICULAR TACHYCARDIA

In the basal state sustained supraventricular tachycardia could not be induced by programmed stimulation in any patient; a non-sustained atrial arrhythmia was induced in five patients from group 1 and in eight from group 2 and a non-sustained paroxysmal junctional tachycardia was induced in five patients from group 2.

After infusion of isoprenaline sustained supraventricular tachycardia could not be initiated in any group 1 patients, even when they had had non-sustained supraventricular tachycardia during the basal study. Non-sustained atrial tachycardia was induced in one group 1 patient who did not have inducible arrhythmia in the basal state.

After isoprenaline sustained junctional tachycardia was induced in 21 patients in group 2a either spontaneously (three) or by programmed stimulation (18). There were 13 re-entrant tachycardias in the atrioventricular node and eight re-entrant tachycardias conducted retrogradely through a Kent bundle. Non-sustained junctional tachycardia was induced in one patient.

After isoprenaline, clinical sustained atrial tachycardia could be reproduced in six patients in group 2 either spontaneously (three) or by programmed stimulation (three). There was one atrial flutter, two atrial fibrillations, and three atrial tachycardias.

In group 2 the sensitivity of the isoprenaline test, defined as the percentage of inducible sustained supraventricular tachycardia, was 90%. Specificity, defined as the percentage of negative tests, was 100% in group 1.

CORRELATION BETWEEN JUNCTIONAL TACHYCARDIA AND ELECTROPHYSIOLOGICAL VARIABLES AND SERUM POTASSIUM (TABLE 5)

We analysed certain variables in patients in group 2a and group 1 to discover whether any of them correlated with the induction of junctional tachycardia.

After isoprenaline we did not find any differences between groups 1 and 2a for variation in cycle length, AH interval, heart rate at which anterograde type 1 second degree block developed, and serum potassium. In group 2a retrograde block was significantly more common after electrophysiological testing in the basal state ($p < 0{\cdot}05$) and after isoprenaline ($p < 0{\cdot}02$) (fig). However, the occurrence of a fast retrograde conduction after isoprenaline did not assist the prediction of the induction of junctional tachycardia: seven patients from group 1 without retrograde conduction in the basal state showed retrograde conduction on isoprenaline at stimulation rates of up to 200/min. The sensitivity of the isoprenaline test defined as the percentage of patients in whom retrograde conduction developed at stimulation rates of 200/min was 86% in group 2a, but its specificity, defined as the percentage that developed retrograde conduction at rates of <200 beats/min was 38% in group 1.

Table 5 *Electrophysiological variables (mean (1SD) before and after isoprenaline in groups 1 and 2a*

	Group 1	*Group 2a*	*p*
CL (ms):			
Before	812 (75)	832 (131)	
Iso	505 (91)	483 (73)	NS
AH (ms).			
Before	82 (21)	86 (23)	NS
Iso	62 (13)	63 (18)	NS
Ant 2nd° block (beats/min)			
Before	173 (39)	169 (35)	NS
Iso	243 (40)	245 (33)	NS
Retr block (beats/min)			
Before	104 (51)	144 (65)	< 0 005
Iso	177 (64)	212 (25)	< 0 02
K^+ (mmol/l).			
Before	4 2 (0 7)	3 9 (0 4)	NS
Iso	3 6 (0 5)	3 3 (0 4)	NS

CL, cycle length, Ant 2nd° block, heart rate at which atrioventricular second degree block occurred; Retr block, heart rate at which ventriculoatrial block occurred, K^+, serum concentration of potassium

ADVERSE EFFECTS OF THE ISOPRENALINE TEST

Arterial blood pressure fell significantly in only one patient. Three patients in group 1 and one in group 2 showed transient sinus bradycardia and a fall in blood pressure several minutes after the beginning of isoprenaline infusion; one of these patients had spontaneous salvoes of atrial tachycardia.

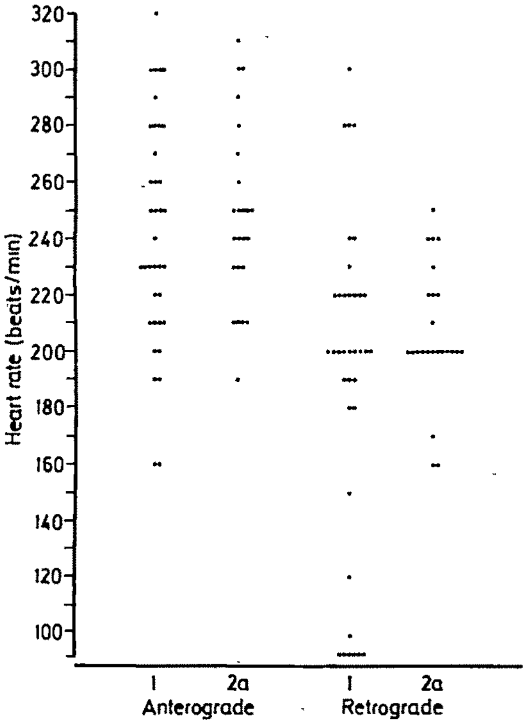


Figure *Heart rates at which anterograde and retrograde type 1 second degree block developed during isoprenaline infusion in groups 1 and 2a.*

One patient from group 2 had spontaneous non-sustained uniform ventricular tachycardia (130 beats/min). The systematic programmed ventricular stimulation induced non-sustained multiform ventricular tachycardia in the basal state in two patients in group 1 and four in group 2. After isoprenaline, none of the patients from group 1 and only two from group 2 had induced multiform non-sustained ventricular tachycardia.

Discussion

We found that the isoprenaline test assisted the diagnosis of catecholamine mediated junctional tachycardias (sensitivity 90%, specificity 100%).

The role of the sympathetic nervous system in supraventricular arrhythmias was suggested by clinical observations, the bicycle exercise test, and 24 hour Holter monitoring.[5] Adrenergic supraventricular tachycardias are induced by exercise or stress, and they occur predominantly during the day. There have been few studies of adrenergic supraventricular tachycardia. The role of adrenergic effects, which modify the refractory periods of accessory pathways, has been studied mainly in Wolff-Parkinson-White syndrome.[4 6 7] Coumel *et al* reported Holter studies to evaluate the role of the sympathetic nervous system in arrhythmias other than in the Wolff-Parkinson-White syndrome.[5] In our study, the sensitivity of Holter monitoring for the diagnosis of adrenergic supraventricular arrhythmia was poor (40%). The sensitivity of exercise testing for triggering a supraventricular tachycardia was also poor (40%). Moreover, when tachycardia occurs immediately after exercise during Holter monitoring, as in cases 15 and 22, the mechanism could be adrenergic or vagal.[8]

These findings indicated the desirability of a pharmacological test that induced trachycardias caused by adrenergic mechanisms. In patients with exercise induced ventricular arrhythmias isoprenaline often caused identical arrhythmia.[9 10] Isoprenaline produces β adrenergic stimulation, which affects the electrophysiological properties of the single cell and the intact heart in several ways.[1-11] In single fibres isoprenaline increased the spontaneous phase IV depolarisation of sinus node, facilitated the development of triggered automaticity, and shortened the action potential duration. In intact hearts, isoprenaline increased the sinus rate and the rate of ectopic pacemakers, accelerated atrioventricular conduction, and shortened the refractoriness of the atrioventricular node and His-Purkinje system. It might be difficult to establish whether the tachycardia induced by isoprenaline resulted from direct stimulation of cardiac β adrenoreceptors or from reflex changes, which might be in the opposite direction, depending on whether the blood pressure rose or fell.[12] Vagal tone may be increased, as in three of our patients, or reduced by the haemodynamic effects of isoprenaline.

An alternative approach to the adrenergic initiation of tachycardia is to use atropine to withdraw the vagal effect, leaving the action of natural catecholamine unopposed. A pharmacological test could also be based on adrenaline, noradrenaline, and atropine.

The frequency with which isoprenaline facilitates the induction of atrial tachycardia has not been reported before. In our study there were six patients with an adrenergic mediated tachycardia that could be reproduced by infusion of isoprenaline and electrophysiological stimulation. The spontaneous occurrence of the arrhythmia in three of them may implicate enhanced automaticity. Non-sustained atrial tachycardia was induced in only one of the controls. Thus infusion of isoprenaline seems a useful provocative test to detect adrenergic paroxysmal atrial tachycardia.

There are few studies of the frequency with which isoprenaline facilitates the induction of junctional tachycardia. Levy *et al* and Hariman *et al* reported two cases of catecholamine dependent atrioventricular nodal reentrant tachycardia[13 14]; Hariman *et al* proposed the enhancement of ventriculoatrial conduction as the mechanism of these tachycardias.[14] In our study, this mechanism was not confirmed. Most reports deal with the induction of junctional tachycardia associated with the Wolff-Parkinson-White syndrome. The spontaneous initiation of reciprocating tachycardia in the Wolff-Parkinson-White syndrome by isoprenaline infusion was reported by Krikler *et al.*[15] Kuck *et al* found a strong correlation between the results of isoprenaline infusion at rest and the results of an exercise test,[16] and in five patients with exercise induced junctional tachycardia, isoprenaline infusion identified the arrhythmia. On the other hand, Brugada *et al* did not find any correlation between the occurrence of isoprenaline induced tachycardias and exercise induced tachycardia.[17] The same results were reported for supraventricular tachycardias.[1 2] The effects of isoprenaline and exercise on the facilitation of arrhythmia do not always coincide: isoprenaline facilitated the induction of arrhythmia in patients with sustained ventricular tachycardia not related to exertion.[2]

In patients who did not have Wolff-Parkinson-White syndrome or spontaneous arrhythmias, we did not find that infusion of isoprenaline increased the induction of non-sustained atrial or ventricular tachycardia. The mechanism by which isoprenaline facilitates the induction of junctional tachycardia remains unknown. Triggered automaticity and delayed after-depolarisation were possible mechanisms for the tachycardia that occurred during isoprenaline infusion in the two patients with spontaneous junctional tachycardia. In the study of Krikler *et al* incessant attacks of tachycardia without antecedent PR prolongation were induced by isoprenaline and were attributed to the speeding of the sinus rate, which might sufficiently shorten the refractory periods of the atrial and anomalous pathways to permit retrograde conduction up the anomalous pathway to the atrium thus causing an echo beat and tachycardia.[15] In most of our patients (n = 19), the arrhythmias required an initiation beat and were stopped by one or two stimuli, suggesting that isoprenaline infusion facilitated reentry by reducing the refractoriness and increasing conduction velocity and the myocardium. The induction of catecholamine dependent reentrant tachycardia has been attributed to a rapid anterograde and/or retrograde conduction[14 18]; this explanation was not confirmed in our study.

Because adrenaline can reproduce stress hypokalaemia[19 20] another mechanism by which isoprenaline might have facilitated reentry was by a reduction in intracellular potassium. The fall in serum potassium, however, was similar in groups 1 and 2, so this mechanism cannot account for the facilitation of arrhythmia.

Infusion of isoprenaline can safely be used to facilitate the induction of supraventricular tachycardia in patients who have spontaneous supraventricular tachycardia, when sympathetic stimulation is enhanced.

We thank Dr R Lazzara for criticisms and advice.

References

1 Reddy CP, Gettes LS. Use of isoproterenol as an aid to electric induction of chronic recurrent ventricular tachycardia. *Am J Cardiol* 1979;77:705–13.

2 Freedman RA, Swerdlow CD, Echt DS, Winkle RA, Soderholm-Difatte V, Mason JW. Facilitation of ventricular tachyarrhythmia induction by isoproterenol. *Am J Cardiol* 1984;54:765–70.

3 Vargas G, Akhtar M, Damato AN. Electrophysiologic effects of isoproterenol on cardiac conduction system in man. *Am Heart J* 1975;90:25–34.

4 Wellens HJJ, Brugada P, Roy D, Weiss J, Barr FW. Effect of isoproterenol on the anterograde refractory

period of the accessory pathway in patients with the Wolff-Parkinson-White syndrome. *Am J Cardiol* 1982;50:180–4.

5 Coumel Ph, Attuel P, Leclercq JF, Friocourt P. Arythmies ventriculaires d'origine vagale ou catécholergique. Effets comparés du traitement béta-bloquant et phénomène d'échappement. *Arch Mal Coeur* 1982; 75:373–88.

6 Levy S, Broustet JP, Clementy J, Vircoulon B, Guern P, Bricaud H. Syndrome de Wolff-Parkinson-White. Corrélations entre l'exploration électrophysiologique et l'effet de l'épreuve d'effort sur l'aspect électrocardiographique de préécitation. *Arch Mal Coeur* 1979; 72.634–40.

7 Strasberg B, Ashley WW, Wyndham CRC, *et al.* Treadmill exercise testing in the Wolff-Parkinson-White syndrome. *Am J Cardiol* 1980;45:742–8.

8 Dimsdale JE, Hartley H, Guiney T, Ruskin JN, Greenblatt D. Post exercise peril. *JAMA* 1984;251:630–2.

9 Gettes LS, Surawicz B. Long term prevention of paroxysmal arrhythmias with propranolol therapy. *Am J Med Sci* 1967;254:257–65.

10 Brembilla-Perrot B, Terrier de la Chaise A, Pichene M, Pernot C, Cherrier F. Valeur diagnostique du test à l'isuprel dans les tachycardies d'effort. *Arch Mal Coeur* 1986;79:302–13.

11 Kassebaum DG, Van Dyke AR. Electrophysiological effects of isoproterenol on Purkinje fibers of the heart. *Circ Res* 1966;19:940–6.

12 Arnold JMO, McDevitt DG. Contribution of the vagus to the haemodynamic responses following intravenous boluses of isoprenaline. *Br J Clin Pharmacol* 1983;15:423–9.

13 Levy S, Pierron JP, Eisinger JF, *et al.* Tachycardie supraventriculaire induite par l'effort et les cathécholamines. *Arch Mal Coeur* 1985;78:1431–6.

14 Hariman RJ, Gomez JAC, El-Sherif N. Catecholamines-dependent atrioventricular nodal reentrant tachycardia. *Circulation* 1983;67:681–6.

15 Krikler D, Curry P, Attuel P, Coumel Ph. "Incessant" tachycardias in Wolff-Parkinson-White syndrome. 1: Initiation without antecedent extrasystoles or PR lengthening, with reference to reciprocation after shortening of cycle length. *Br Heart J* 1976;38: 885–96.

16 Kuck K-H, Kunze KP, Roewer N, Bleifeld W. Electrophysiologic studies after isoproterenol and at exercise in patients with exercise induced circus movement tachycardia [Abstract]. *Circulation* 1983; 68(suppl III):76.

17 Brugada P, Facchini M, Wellens HJJ. Effects of isoproterenol and amiodarone and the role of exercise in initiation of circus movement tachycardia in the accessory atrioventricular pathway. *Am J Cardiol* 1986;57:146–9.

18 Waxman MB, Wald RW. Effects of autonomic tone on tachycardias. In: Surawicz B, Reddy CP, Prystowski EN, eds. *Tachycardias.* Boston: Martinus Nijhoff, 1984:67–99.

19 Brown MJ. Hypokalemia from beta 2-receptors stimulation by circulating epinephrine. *Am J Cardiol* 1985;56:3D–5D.

20 Struthers AD, Reid JL, Whitesmith R, Rodger JC. Effect of intravenous adrenaline on electrocardiogram, blood pressure, and serum potassium. *Br Heart J* 1983;49:90–3.

Br Heart J 1989;61:356–7

Endocarditis in intravenous drug abusers with staphylococcal septicaemia

JENNIFER M A BURNS, K J HOGG, W S HILLIS, F G DUNN

From the Departments of Cardiology and Materia Medica, Stobhill General Hospital, Glasgow

SUMMARY The case reports of 186 intravenous drug abusers admitted over a three year period were studied. Nineteen had proven staphylococcal septicaemia. Echocardiography showed tricuspid vegetations in seven and aortic vegetations in two. Eighteen out of 19 had systolic murmurs, but only the two patients with aortic vegetations had diastolic murmurs. The chest *x* ray showed opacities in 10 patients (all those with tricuspid vegetations plus three with normal echocardiograms). Four patients died during follow up, including both those with aortic vegetations; both mitral and tricuspid vegetations were found at necropsy in the other two. All remaining patients were alive at one year.

The presence of tricuspid vegetations in intravenous drug abusers is associated with opacities on chest *x* ray, but carries a good short term prognosis. But these results suggest a poor outcome when left sided endocarditis is present in intravenous drug abusers.

Endocarditis is a well recognised complication in heroin addicts who use the intravenous route. Such endocarditis may be difficult to distinguish from staphylococcal septicaemia without cardiac involvement. We have assessed the relative merits of clinical and investigative techniques in the cardiac assessment of intravenous drug abusers with documented staphylococcal septicaemia.

Patients and methods

In a retrospective review of case records for the years 1984–1986 inclusive, we found 186 admissions of intravenous drug abusers to Stobhill General Hospital, Glasgow, and to the local infectious diseases hospital, Ruchill Hospital. Of these, 19 had proven staphylococcal septicaemia. The mean age of these 15 men and four women was 24 (range 18–35). All 19 had had echocardiographic studies by M mode and cross sectional techniques. These studies were reviewed by two independent observers who were asked to comment on the presence or absence of valve vegetations. A vegetation was defined as a non-uniform "shaggy" echogenic mass attached to the valve leaflet (figure). These findings were compared with the clinical condition, chest *x* ray findings, and outcome in each patient (table).

Results

Ten of the 19 patients had a normal echocardiogram. Seven had tricuspid vegetations and two had aortic vegetations. A review of the case notes showed that 18 of the 19 patients were reported to have a systolic murmur. Two patients had diastolic murmurs and both of them had aortic vegetations.

When the chest *x* rays were reviewed, opacities suggestive of septic pulmonary emboli were found in seven patients with tricuspid vegetations and three with normal echocardiograms. None of the remaining patients, including those with aortic vegetations, had abnormal lung fields.

The outcome of the patients was assessed. All 10 of those patients with a normal echocardiogram left hospital after an apparent recovery, although further follow up found that one died over a year later after operation for endocarditis of the mitral and tricuspid valves. Follow up was for a minimum of 18 months. Of the seven patients with tricuspid vegetations, one died on his first hospital admission. At necropsy he too was found to have mitral valve endocarditis in addition to tricuspid valve disease. Both patients with aortic valve disease died, although not on their first hospital admission. The cause of death in one was cardiac failure with pulmonary emboli. At

Requests for reprints to Dr F G Dunn, Department of Cardiology, Stobhill General Hospital, Glasgow G21 3UW.

Accepted for publication 10 January 1989

Table *Findings and outcome in 19 intravenous drug abusers with staphylococcal septicaemia*

	Patients (n = 19)	*Systolic murmur*	*Diastolic murmur*	*Chest x ray opacities*	*Deaths*
Normal echocardiogram	10	10	0	3	1
Tricuspid vegetations	7	7	0	7	1
Aortic vegetations	2	1	2	0	2

necropsy his aortic valve was found to be bicuspid. The other patient died suddenly.

Discussion

Staphylococcal septicaemia is a well recognised sequela of intravenous drug abuse[1] but it may be difficult to determine whether this is complicated by infective endocarditis. We found that systolic murmurs were unhelpful in establishing the diagnosis of endocarditis; both patients with aortic vegetations had diastolic murmurs, however. Clearly, the demonstration of vegetations by echocardiography confirms the diagnosis of endocarditis, but echocardiography may give false negative results.[2] We found that all seven patients with tricuspid vegetations had opacities on chest *x* ray but only three out of 10 patients with normal echocardiograms did. We therefore believe that if opacities are seen on the chest *x* ray, serial echocardiograms should be obtained and the patient should be treated as for endocarditis. It has previously been suggested that the triad of intravenous drug addiction, staphylococcal septicaemia, and pulmonary embolism is pathognomic for tricuspid valve endocarditis.[3]

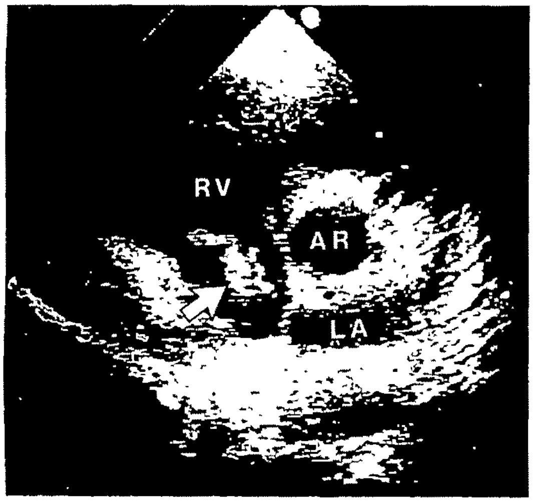


Figure *A parasternal short axis cross sectional echocardiogram. Arrow indicates the tricuspid vegetation. RV, right ventricle; AR, aortic root; LA, left atrium.*

The tricuspid vegetations were well tolerated—there were no early deaths in patients with isolated tricuspid vegetations. Follow up of these patients is difficult, but four of the six survivors with tricuspid vegetations have had repeat echocardiography, on average 18 months later. In all the vegetations had disappeared, but the tricuspid valve appeared thickened. Only one patient had clinical signs of mild right heart failure and tricuspid incompetence. Since the formal study has ended, a further three patients have been seen with the triad of staphylococcal septicaemia, pulmonary opacities, and tricuspid vegetations, and have all survived without sequelae.

In contrast, we confirmed the poor prognosis in those with left sided endocarditis.[1] We have now seen four such patients, none of whom has survived more than a year after the diagnosis was made. We do not believe that operation is an option in these patients unless there is clear evidence that they have overcome their addiction.

Echocardiography is of unquestionable value in the diagnosis of endocarditis in intravenous drug abusers. Tricuspid endocarditis should be strongly considered as a diagnosis in staphylococcal septicaemia if there are opacities on chest *x* ray, even when the echocardiogram is normal. The prognosis in left sided endocarditis is poor, whereas patients seem to tolerate the presence of tricuspid vegetations, at least in the short term.

References

1 Espersen F, Frimodt-Moller N. Staphylococcal aureus endocarditis: a review of 119 cases. *Arch Intern Med* 1986;146:1118–21.

2 Come PC, Isaacs RE, Riley MF. Diagnostic accuracy of M-mode echocardiography in acute endocarditis and prognostic implications of ultrasound vegetations. *Am Heart J* 1982;103/5:839–41.

3 Julander I, Arneborn P, Back E, Hoglund C, Svanbom M. Intravenous drug addiction—staphylococcal septicaemia—pulmonary embolism: a triad pathognomic for tricuspid valve endocarditis? *Scand J Infect Dis* 1983;15:257–65.

Br Heart J 1989;**61**:358–60

Aortic valvotomy for critical aortic stenosis in neonates and infants aged less than one year

SESHADRI BALAJI, BARRY R KEETON, GEORGE R SUTHERLAND, DARRYL F SHORE, JAMES L MONRO

From the Wessex Cardiothoracic Centre, Southampton General Hospital, Shirley, Southampton

SUMMARY Between April 1974 and December 1987, 20 infants (six under one month of age) (mean weight 4·9 kg) underwent surgical valvotomy for critical aortic stenosis. Three of the four patients treated before 1976 died. Since 1979, 16 infants (four neonates) have undergone valvotomy with no deaths. Mortality for the whole group was 15%; in the neonates it was 33%. There were no late deaths. The survivors were followed up for a mean of 3 years 9 months and two required re-operations.

The considerable improvement in surgical results in the past decade should be taken into account when newer techniques such as balloon dilatation are evaluated.

Critical aortic stenosis in infancy has been associated with high mortality and morbidity.[1-3] Medical treatment alone is unsuccessful. Surgical valvotomy is successful to varying degrees in relieving the stenosis but in infancy it is only palliative and all patients will later require replacement of the aortic valve or root. There has been recent interest in the use of balloon dilatation for this condition.[4-6] This is why it is important to analyse the results of surgical valvotomy so that the risks to the patient of the various forms of treatment can be established.

This paper reviews our experience with surgical valvotomy in aortic stenosis.

Patients and methods

Between April 1974 and December 1987, 20 infants including six neonates underwent aortic valvotomy for critical or severe aortic stenosis at Southampton General Hospital. Age at surgery ranged from one day to 51 weeks (mean 14 weeks, median eight weeks). Weight at surgery ranged from 2·5 to 10 9 kg (mean 4·9 kg). Ten patients required emergency surgery and eight of them were moribund before operation with poor perfusion and acidosis and a mean pH of 7·25. Of the other 12, three were symptom free while all the rest had signs of heart failure. Two patients with symptoms had already had an operation: one who had valvotomy at 11 months had had repair of coarctation at the age of two months and repair of ventricular septal defect at three months and the other had undergone repair of coarctation with ligation of the ductus.

The electrocardiogram showed left ventricular hypertrophy in 13 with strain pattern in three. Chest *x* ray showed a cardiothoracic ratio of 0·47–0 76 (mean 0·61). Before 1984 all patients underwent cardiac catheterisation, but since then, of ten patients treated, all but three had an operation on echocardiographic grounds alone. Retrospective analysis of the angiogram and/or the echocardiogram showed small left ventricles in three, dilated ventricles in six, and normal sized ventricles in the rest. The left ventricular ejection fraction measured in 15 patients (on the angiogram in five and the echocardiogram in 10) ranged from 10% to 80% (mean 45%). The pressure gradient across the aortic valve measured in 15 patients (by catheter in seven and Doppler in eight) ranged from 33 mm Hg to 120 mm Hg (mean 76 mm Hg).

All patients underwent aortic valvotomy under cardiopulmonary bypass and moderate hypothermia. Cardioplegia was used in all but the first four patients who were treated before 1979. At operation eight patients had tricuspid aortic valves and the rest were bicuspid. Associated lesions corrected at the same operation included ligation of the ductus arteriosus in three, closure of atrial septal defect in two, and repair of coarctation of aorta through a second (left

Requests for reprints to Mr James L Monro, FRCS, Wessex Cardiothoracic Centre, Level E, East Wing, Southampton General Hospital, Shirley, Southampton SO9 4XY.

Accepted for publication 10 January 1989

Table *Data on 20 infants who had valvotomy*

Patient	*Age*	*Associated lesion*	*Cardiac catheterisation before operation*	*AV gradient (mm Hg)*		*LVEF (%)*		*Pre-op state*	*Pre-op pH*	*Outcome*	*Re-op*	*AR*	*EFE*
				Before	*After*	*Before*	*After*						
1	16 wk		Yes	37	—	—	—	M	7 38	Died		–	+
2	33 wk		Yes	—	43	66	70	CF	—	Alive		+	
3	3 days	ASD	Yes	56	—	—	—	M	7 01	Died		–	+
4	3 days	ASD	Yes	—	—	33	—	M	7 0	Died		–	+
5	19 wk		Yes	53	25	14	70	CF	7 41	Alive		+ +	
6	7 wk		Yes	60	40	—	89	M	7·26	Alive		+ +	
7	44 wk	COA, VSD	Yes	80	60	76	70	CF	—	Alive	Yes	+	
8	37 wk		Yes	—	35	36	50	CF	7 4	Alive		–	+
9	9 wk		Yes	33	40	23	82	M	7 2	Alive		+ +	
10	29 wk		Yes	80	40	71	54	SF	7 21	Alive		–	
11	12 wk		—	—	30	34	—	M	7 6	Alive		–	
12	5 days	DA	Yes	—	30	40	52	M	7 3	Alive		+	+
13	1 day	DA	—	100	50	80	73	M	7 23	Alive		–	
14	6 wk	COA	Yes	100	40	58	60	CF	7 43	Alive		–	
15	11 wk		—	40	60	—	50	SF	7 42	Alive		–	
16	5 wk	COA, DA	Yes	100	35	10	62	CF	7 55	Alive	Yes	+	+
17	5 wk		—	120	100*	45	89	CF	7 4	Alive		–	
18	51 wk		—	100	40	—	60	CF	7 52	Alive		+	
19	3 wk		—	36	35	53	97	CF	7 58	Alive		–	
20	5 days		—	40	25	36	67	SF	7 59	Alive		–	

*Dynamic left ventricular obstruction.
AR, aortic regurgitation; ASD, atrial septal defect, AV, aortic valve, CF, cardiac failure; COA, coarctation aorta; DA, ductus arteriosus, EFE, endocardial fibroelastosis; LVEF, left ventricular ejection fraction; M, moribund, SF, symptom free, VSD, ventricular septal defect, + = mild, + + = moderate

thoracotomy) incision in one patient (table). Two had previously undergone coarctation repair, one of whom also had ductus ligation. One of these had a ventricular septal defect closed at a further operation before aortic valvotomy.

Results

Three of the four patients treated before 1976 died and there have been no deaths since. All the infants who died did so within 24 hours of operation. At the time of operation, two of them (both three days old) were desperately ill; necropsy showed severe widespread endocardial fibroelastosis. The third, a girl aged four months, had had three cardiac arrests at cardiac catheterisation just before operation.

Mortality for the whole group was 15%, and for the neonates it was 33%. Since 1979, 16 infants including four neonates have been treated. None has died.

Patients spent 1–13 days (mean three) in intensive care after operation, and ten patients spent longer than 48 hours. Ten patients needed inotropic support for from one hour to six days, and five of them required inotropes for over 48 hours. Intubation and ventilation was continued for longer than 48 hours in five patients (maximum five days). Follow up of the 17 survivors ranged from two months to 12 years (mean of 3 years 8 months). Two have required reoperations—one for resection of fibrous subaortic stenosis and one aortic root replacement for severe residual aortic stenosis. Five children still have symptoms and effort intolerance and seven are on medication to counter heart failure. There were no late deaths.

The most recent electrocardiogram showed left ventricular hypertrophy in eight patients with strain pattern in one, and the chest *x* ray showed cardiothoracic ratios ranging from 0·47 to 0·73 (mean 0·57). Doppler estimation of residual aortic stenosis showed gradients ranging from 25 to 100 mm Hg (mean 43 mm Hg). The valvar gradient was less than 60 mm Hg in all but three: 60 mm Hg in two and another had a dynamic subvalve left ventricular outflow tract gradient of 100 mm Hg on Doppler which was not present at cardiac catheterisation under general anaesthesia. Eight had aortic regurgitation (mild in five and moderate in three). The left ventricular ejection fraction estimated by echocardiography in 16 survivors ranged from 50 to 97% (mean 68%).

None of the patients has had neurological complications caused by their primary cardiac problem or as a result of operation.

Discussion

Widely varying mortality ranging from 9% to 66% has been reported for aortic valvotomy under either conventional cardiopulmonary bypass or inflow occlusion.[1 7 8] The major determinants of mortality are the patient's preoperative clinical state, the size of the left ventricle and aortic annulus, the presence of associated anomalies and, in particular, the presence of mitral stenosis and endocardial fibroelastosis.[8 9] The lesion is a variant of the hypoplastic left heart syndrome and in borderline cases categorisation is subjective.

Alternatives to open valvotomy include closed transventricular valvotomy without bypass and percutaneous balloon dilatation. Although there is less experience with transventricular valvotomy, the results are comparable to open valvotomy.[9-11] Balloon dilatation has produced good results in some patients,[4 5] but has damaged the aortic valve and root in others.[12 13] Wren *et al* reported a series of thirteen neonates and infants who underwent percutaneous balloon dilatation in which there were five early and two late deaths.[6] Their children, however, are not strictly comparable with our series. They were smaller and more unwell, two had already undergone surgical valvotomy and two died at subsequent operation.

Clearly, operation is the only alternative when the aortic valve cannot be crossed at catheterisation. Whereas, in theory, open valvotomy might be expected to be more controlled and give better results, proponents of transventricular valvotomy argue that the gelatinous and dysplastic nature of the valve in infants with aortic stenosis makes it unlikely that direct visualisation of the valve would influence the results.[9] We feel that open valvotomy allows the surgeon to perform a careful commissurotomy in all cases and that direct visualisation helps to decide where and how far the incision ought to run. We believe that our low rates of clinically significant restenosis and regurgitation show that a good balance can be achieved between too large or too small a commissurotomy.

In each series a small proportion of patients needs early re-operation for residual stenosis or regurgitation, and all patients are expected to need replacement of the aortic valve or root in due course. The main advantage of percutaneous balloon dilatation is expected to be the absence of adhesions in the thorax at definitive operation. Also, balloon dilatation can be repeated several times to achieve success. Repeated attempts risk damage to the aortic wall, valve or the femoral artery, however. Also, when balloon dilatation fails the condition of the infant might deteriorate during the procedure. On the other hand, if balloon dilatation is limited to children who are thought to be unsuitable or unfit for operation the risk associated with the procedure would increase, as shown by the results of Wren *et al.*[6] Eight of our patients (of whom five survived) were moribund (mean pH 7·25) and might in some centres have been deemed unsuitable for operation. We showed that good results can be achieved even in these very sick infants.

The various methods available for the relief of infant aortic stenosis have their advantages and disadvantages, but which is the best method in children whose condition is stable and who have no adverse features? Newer techniques such as balloon dilatation will need further evaluation before the answer is known and such an assessment must take into account the improved results for valvotomy.

The results of valvotomy have improved significantly in the past decade as shown by our figures and those of Messina *et al* who reported one operative and no late deaths in 11 neonates.[7]

Until we know more about the results of new techniques, valvotomy will remain the most suitable method for the relief of infant aortic stenosis. The fact that an infant is "too unwell" is no reason to attempt balloon dilatation rather than valvotomy.

References

1 Keane JF, Bernard WF, Nadas AS. Aortic stenosis surgery in infancy. *Circulation* 1975;52.1138–43.

2 Kugler JD, Campbell E, Vargo TA, McNamara DG, Hallman GL, Cooley DA. Results of aortic valvotomy in infants with aortic valvular stenosis. *J Thorac Cardiovasc Surg* 1979;78:553–8.

3 Edmunds LH, Wagner HR, Heymann MA. Aortic valvotomy in neonates. *Circulation* 1980;61.421–7.

4 Lababidi Z, Weinhaus L. Successful balloon valvuloplasty for neonatal critical aortic stenosis. *Am Heart J* 1986;112:913–6.

5 Rupprath G, Neuhaus KL. Percutaneous balloon valvuloplasty for aortic valve stenosis in infancy. *Am J Cardiol* 1985;55:1655–6.

6 Wren C, Sullivan I, Bull C, Deanfield J. Percutaneous balloon dilatation of aortic valve stenosis in neonates and infants *Br Heart J* 1987;58·608–12.

7 Messina LM, Turley K, Stanger P, Hoffman JIE, Ebert PA. Successful aortic valvotomy for severe congenital valvular aortic stenosis in the newborn infant. *J Thorac Cardiovasc Surg* 1984;88.92–6.

8 Pelech AN, Dyck JD, Trusler GA, *et al.* Critical aortic stenosis, survival and management *J Thorac Cardiovasc Surg* 1987;94:510–7.

9 Duncan K, Sullivan I, Robinson P, Horvath P, de Leval M, Stark J. Transventricular aortic valvotomy for critical aortic stenosis in infants. *J Thorac Cardiovasc Surg* 1987;93:546–50.

10 Midgley FM, Perry LW, Shapiro SR, *et al.* Closed transventricular valvotomy for critical aortic stenosis in the neonate. In. Doyle EF, Engle MA, Gersony WM, Rashkind WJ, Talner NS, eds. *Paediatric cardiology Proceedings of the second world congress* New York: Springer Verlag, 1986:540–1.

11 Trinkle JK, Norton JB, Richardson JD, Grover FL, Noon JA. Closed aortic valvotomy and simultaneous correction of associated anomalies in infants. *J Thorac Cardiovasc Surg* 1975;69:758–62.

12 Phillips RR, Gerlis LM, Wilson N, Walker DR. Aortic valve damage caused by operative balloon dilatation of critical aortic valve stenosis. *Br Heart J* 1987; 57·168–70.

13 Waller BF, Girod DA, Dillon JC. Transverse aortic wall tears in infants after balloon angioplasty for aortic valve stenosis. *J Am Coll Cardiol* 1984;4: 1235–41.

Addendum

We have operated on a further seven infants aged from five days to four months (mean 6 weeks) including three in the first week of life. One 36 week preterm infant aged six days, weighing 2 4 kg, who also had mitral stenosis and endocardial fibroelastosis died 56 days after the operation, having never left the intensive care unit. The rest survived and are well.

Br Heart J 1989;61:361–4

Diagonal earlobe creases and fatal cardiovascular disease: a necropsy study

N KIRKHAM, T MURRELLS,* D H MELCHER, E A MORRISON

*From the Department of Pathology, Royal Sussex County Hospital, Brighton and the *Epidemiology and Public Health Research Unit, Robens Institute, University of Surrey, Guildford*

SUMMARY The association between diagonal earlobe creases and fatal cardiovascular disease was investigated in a consecutive series of 303 coroner's necropsies. Those studied all died outside hospital in the Brighton Health District. Data were analysed on the cause of death and on the type of earlobe, the presence or absence of diagonal creases, age, sex, height, and any previous history of cardiovascular disease or diabetes mellitus. The age of nine men and six women was not known. Cardiovascular causes of death included ischaemic and hypertensive disease, calcific valvar stenosis, ruptured dissecting aneurysm of the thoracic aorta, and ruptured atheromatous aneurysm of the abdominal aorta. The mean (SD) age at death was 72 (15) and the male to female ratio was 1·3:1. Diagonal creases were present in 123 (72%) of 171 men and 88 (67%) of 132 women. A previous history of cardiovascular disease was present in 90 (30%) of the total of 303 and 74 (35%) of the 211 with diagonal creases. A cardiovascular cause of death was present in 154 (73%) of 211 with and 41 (45%) of 92 without diagonal creases and was associated with an increased risk of a cardiovascular cause of death of 1·55 in men and 1·74 in non-diabetic women.

The Emperor Hadrian probably died of cardiovascular disease. Several busts, now in European museums, show quite distinct diagonal creases on both of his earlobes.[1] Diagonal earlobe creases run from the lower pole of the external meatus, diagonally backwards to the edge of the lobe at approximately 45° (figure), and have been associated with cardiovascular disease in several clinical studies.[2–13] We studied a series of coroner's necropsy cases to see whether diagonal earlobe creases are associated with fatal cardiovascular disease.

Patients and methods

Data were collected from unselected consecutive necropsies conducted on behalf of HM Coroner on adults at the Brighton Borough Mortuary by three consultant pathologists. These people had died within the Brighton Health District in circumstances in which it was not possible to issue a death certificate. Before the pathologist arrived in the mortuary to perform the necropsy, at least two of the three members of the mortuary staff examined the ears. They classified the earlobe as soldered, attached, or free by comparing them with figure 1 in the paper by Overfield and Call.[14] They used the definition of Brues: "The free lobe is attached only to the ear, not to the side of the face in front of and below the ear. The attached lobe blends into the back of the cheek; and soldered lobe is an extreme version of the attached form".[15] The presence or absence of a diagonal crease on one or both ears was then recorded, together with details of age, sex, and height. The presence of a crease was only recorded if an unequivocal single crease was present, running diagonally backwards and downwards across the lobe from the external meatus. A photocopy of the figure in Frank's letter was used as a standard.[2]

After performing the necropsy the pathologist recorded the principal cause of death and classified it as cardiovascular or non-cardiovascular. This was done without taking the earlobe appearances into account. The presence or absence of a history of heart disease or diabetes mellitus was recorded from information supplied by the coroner's officers from their interviews with witnesses to the deaths and with the next of kin, which included details of all prescribed or proprietary medicines found in association with the subjects.

Requests for reprints to Dr N Kirkham, Department of Pathology, Royal Sussex County Hospital, Brighton BN2 5BF.

Accepted for publication 19 January 1989

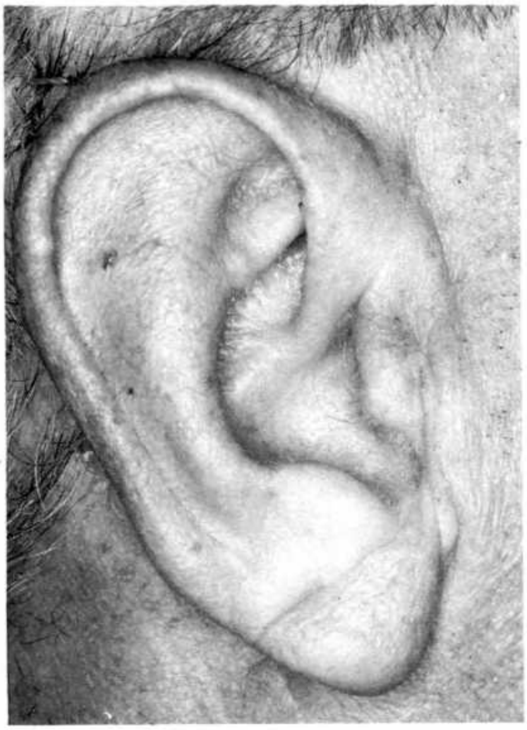


Fig *Diagonal earlobe crease.*

Table 1 *Earlobe type and diagonal creases*

Lobe type	*Crease*	*No crease*	*All*
Soldered	7	2	9
Attached	131	65	196
Free	73	25	98
Total	211	92	303

We investigated the relation between earlobe crease, age at death, height at death, diabetes, earlobe type, and the ratio of risks (RR) of cardiovascular cause of death, using the method proposed by Wacholder[16] for the regression estimation of ratios of risk as defined by Armitage.[17] These risk factors were fitted simultaneously into a regression model to identify those that were significantly related to the risk of cardiovascular cause of death while keeping the effects of all other risk factors constant. A model that included the best predictors was chosen. We did not use odds ratios because approximations of relative risk when the proportion of subjects with cardiovascular disease is high tend to invalidate this approach.

Results

Data from 303 necropsies were collected. The age of 15 people was not known. The mean (SD) age of the group was 72·2 (14·7). Details of age were available for 288 people: 162 men (mean (SD) age 70·3 (12·8) and 126 women (74·6 (16·6)).

Most of the earlobes were of medium size and classified as attached; creases were slightly more common on the larger free type than on the attached type (table 1). The diagonal creases were easily recognised: the mortuary staff always agreed on whether they were present or absent. Creases were less common in those aged $\leqslant$ 55. The frequency of creases remains fairly constant with increasing age in subjects from 55 years of age upwards (table 2). The proportion of creases at necropsies in those aged $\geqslant$ 55 (191/260) was significantly higher than in the younger subjects (11/28) (74% *v* 39%, $p < 0.001$, 95% confidence interval for the difference in proportions 17% to 52%). The proportion of creases in males and females was similar (123/171 (72%) *v* 88/132 (67%), 95% confidence interval for the difference in proportions −5% to 16%). A history of cardiovascular disease was present in 35% (47/211)

Table 2 *Number of people with a cardiovascular cause of death (total deaths in brackets) by age, sex, and presence or absence of a crease*

	Age					
Crease	*<55*	*55–64*	*65–74*	*75–84*	*85+*	*All**
Men:						
Present	5 (7)	13 (16)	35 (45)	34 (39)	7 (10)	99 (123)
Absent	1 (8)	6 (8)	11 (14)	4 (12)	3 (3)	26 (48)
RR	5·71	1·08	0·99	2·62	0·70	1·49
(95% CI)	(0·86 to 37·9)	(0·68 to 1·72)	(0·72 to 1·36)	(1·16 to 5·87)	(0·47 to 1·05)	(1·13 to 1·96)
Women:						
Present	0 (4)	5 (9)	10 (13)	23 (36)	15 (23)	55 (88)
Absent	1 (9)	0 (1)	2 (6)	7 (15)	4 (10)	15 (44)
RR	3·85		2·31	1·37	1·63	1·83
(95% CI)	(0·53 to 27·9)		(0·72 to 7·44)	(0·76 to 2·48)	(0·72 to 3·69)	(1·18 to 2·85)

*There was no record of the age of 15 people.
CI, confidence interval; RR, ratio of risks.

Table 3 *Cardiovascular causes of death*

Principal cause of death	*No*
Ischaemic/hypertensive	152
Abdominal aneurysm	15
Thoracic aneurysm	10
Calcific aortic valve stenosis	10
Cor pulmonale	6
Cardiomyopathy	2
Total	195

of those with creases compared with 17% (16/92) of those without.

CAUSES OF DEATH

Cardiovascular causes of death were classified into six groups (table 3). Most deaths were the result of ischaemic and/or hypertensive disease. In addition, there were smaller groups with other principal cardiovascular causes of death; this may extend the number of possible cardiovascular conditions associated with diagonal earlobe creases.

In men, earlobe crease, diabetes, and height in those without a crease were predictive of cardiovascular death (table 4). For men of an average height at death of 175 cm the risk of a cardiovascular cause of death was 1·55 (95% confidence interval 1·15 to 2·10) times higher in those men with a crease than in those without a crease. Height was analysed as a continuous variable and did not appear to increase the risk of a cardiovascular cause of death in those men with a crease, but increasing height increased the risk in those without a crease. For women, age at death, diabetes, and creases in non-diabetics were predictive of a cardiovascular cause of death. Creases in diabetic women were not predictive. In non-diabetic women with an average age at death of 75 years the risk of cardiovascular cause of death was 1·74 (95% confidence interval 1·08 to 2·79) times higher when a crease was present.

Table 4 *Log relative risk estimates from the "best" models for men and women*

	Beta (log relative risk)	*Standard error*	*p*
Men:			
Crease	0·441	0·154	0·0042
*Height	0·238	0·054	0·0001
Diabetes	0·212	0·068	0·0018
Crease and height interaction	−0·249	0·066	0·0002
Women			
Crease	0·551	0·243	0·023
*Age (linear)	0·224	0·100	0·025
*Age (quadratic)	−0·294	0·129	0·022
Diabetes	0·936	0·230	0·0001
Crease and diabetes interaction	−0·579	0·243	0·017

*Height and age were standardised to have mean zero and SD of one, separately for men and women

Discussion

In 1973 Frank drew attention to the association between diagonal earlobe creases and coronary heart disease.[2] The creases on his patients' ears were usually bilateral and were associated with an increased number of other risk factors for coronary heart disease and with premature onset of the disease. He concluded that the presence of creases was a particularly useful marker of cardiovascular disease in those aged < 60, a finding subsequently confirmed by Gral and Thornburg.[3]

Other workers have shown that up to 90% of patients with creases undergoing coronary angiography have significant disease.[4] The creases are not usually present in childhood but develop during life, are not associated with diabetes, and should be regarded as a coronary risk factor.[5] They become more common with age, with the greatest increase in the fifth decade,[6 7] and are associated with increased degrees of coronary artery sclerosis.[5]

Creases tend to develop with coronary heart disease.[3 8 9] This close relation seems to be independent of age but may be associated with a previous history of myocardial infarction. The exceptions to this are "Oriental patients, native American Indian patients, and children with Beckwith's syndrome."[10]

The possibility of an underlying genetic factor has been considered. A threefold increase in HLA-B27 has been shown and an association with the C3-F atherosclerosis gene[11] and chromosome 11[18 19] has been suggested.

In a study of Japanese and American men aged 54–70 creases were found in 30% of subjects and were associated with obesity and systemic hypertension. A relation between creases and obesity rather than between creases and coronary heart disease was inferred.[12] Others have not found an association with obesity or with smoking, raised serum cholesterol, decreased high density lipoproteins, or systemic hypertension.[13]

We found a strong association between earlobe creases and a cardiovascular cause of death in men and women after age, height, and diabetes had been controlled for. Earlobe creases did not seem to increase the risk of a cardiovascular cause of death in diabetic women. We were not able to study the effect of obesity, but we saw as many creases on thin as fat people. The excess of elderly subjects reflects the fact that this was a group of people who had died suddenly and unexpectedly while living in the community. Although some may have been receiving treatment as hospital inpatients, none was in hospital at the time of death. In addition to coronary heart disease, we found that those with other fatal cardiovascular diseases such as ruptured aortic aneurysms also tended to have earlobe creases.

The presence of the combination of a previous history of cardiovascular disease and earlobe creases was not as strongly associated with cardiovascular causes of death as the presence of an earlobe crease alone. This suggests that cardiovascular disease was being underdiagnosed in this population. We conclude that diagonal earlobe creases are associated with cardiovascular causes of death.

We thank the staff of the Brighton Borough Mortuary for their help in collecting the data for this study.

References

1 Petrakis NL. Diagonal earlobe creases, type A behaviour and the death of Emperor Hadrian. *West J Med* 1980;**132**:87–91.

2 Frank ST. Aural sign of coronary-artery disease. *N Engl J Med* 1973;**289**:327–8.

3 Gral T, Thornburg M. Earlobe creases in a cohort of elderly veterans. *J Am Geriatr Soc* 1983;**31**:134–6.

4 Sternlieb JJ, Gau TG, Davis GD, Rutherford BD, Frye RL. The ear crease sign in coronary artery disease. *Circulation* 1974;suppl III:152.

5 Lichstein E, Chapman I, Gupta PK, *et al.* Diagonal ear-lobe crease and coronary artery sclerosis *Ann Intern Med* 1976;**85**:337–8.

6 Mehta J, Hamby RI. Diagonal ear-lobe creases as a coronary risk factor. *N Engl J Med* 1974;**291**:260.

7 Christiansen JS, Mathiesen B, Andersen AR, Calberg H. Diagonal ear-lobe crease in coronary heart disease. *N Engl J Med* 1975;**293**:308–9.

8 Kaukola S. The diagonal ear-lobe crease, heredity and coronary heart disease. *Acta Med Scand* 1982;**668**(suppl).60–3.

9 Jorde LB, Williams RR, Hunt SC. Lack of association of diagonal earlobe creases with other cardiovascular risk factors. *West J Med* 1984;**140**:220–3.

10 Elliott WJ. Ear lobe crease and coronary artery disease. 1,000 patients and review of the literature. *Am J Med* 1983;**75**:1024–32.

11 Kristensen BO. Ear-lobe crease and vascular complications in essential hypertension. *Lancet* 1980;i:265.

12 Rhoads GG, Klein K, Yano K, Preston H. The earlobe crease—sign of obesity in middle-aged Japanese men. *Hawaii Med J* 1977;**36**:74–7.

13 Kaukola S, Manninen V, Valle M, Halonen PI. Ear-lobe crease and coronary atherosclerosis. *Lancet* 1979;ii:1377.

14 Overfield T, Call EB. Earlobe type, race, and age: effects on earlobe creasing. *Am J Geriatr Soc* 1983;**31**: 479–81.

15 Brues AM. *People and races.* New York: Macmillan, 1977:118.

16 Wacholder S. Binomial regression in GLIM: estimating risk ratios and risk differences. *Am J Epidemiol* 1986;**123**:174–84.

17 Armitage P. *Statistical methods in medical research.* Oxford: Blackwell Scientific Publications, 1971: 426–33.

18 Jarrett RJ. Atherosclerosis, the earlobe crease, and chromosome II. *Lancet* 1984;i:513.

19 Dang CV. The earlobe crease: chromosomes, acupuncture, and atherosclerosis. *Lancet* 1984;i:1083.

Br Heart J 1989;**61**:365–7

Case reports

Perinatal management of critical aortic valve stenosis diagnosed by fetal echocardiography

MURRAY A ROBERTSON, PAUL J BYRNE, PATRICIA A PENKOSKE

From the Divisions of Pediatric Cardiology, Newborn Medicine, and Pediatric Cardiothoracic Surgery, Walter C Mackenzie Health Sciences Centre, Edmonton, Alberta, Canada

SUMMARY A case of critical aortic valve stenosis was diagnosed in utero by echocardiography and managed successfully by early elective caesarean section and aortic valvotomy.

Critical aortic valve stenosis is infrequently diagnosed in utero, and is associated with a high neonatal mortality rate.[1 2] Fetal echocardiography is a reliable technique for the diagnosis of abnormalities of fetal cardiac morphology and function.[3 4] To date, however, this technique has not appreciably influenced the mortality associated with congenital cardiac lesions. Neonates with critical aortic valve stenosis commonly develop severe congestive heart failure with poor cardiac output and associated metabolic acidosis within the first few hours of life. Despite vigorous emergency medical treatment, these infants often remain critically ill and this increases the perioperative morbidity and mortality of subsequent aortic valvotomy.

We report a case of critical aortic valve stenosis diagnosed in utero at 32 weeks' gestation that was managed by early elective caesarean section at 36 weeks' gestation. Surgical aortic valvotomy performed shortly after delivery was successful.

Case report

A 29 year old woman (gravida 2, para 1) was referred to the paediatric echocardiographic laboratory for a fetal cardiac assessment at 32 weeks' gestation. A previous fetal ultrasound for suspected polyhydramnios at 30 weeks had shown a dilated, poorly contractile left ventricle. Echocardiographic studies showed increased left ventricular dimensions with an end diastolic diameter of 20 mm and a shortening fraction of 15%. Normal left ventricular diameter and shortening fraction for this gestational age are approximately 14 mm and 37% respectively.[5] The aortic valve appeared thickened and dysplastic with reduced mobility. Pulsed wave Doppler interrogation in the ascending aorta immediately distal to the aortic valve did not establish whether or not there was anterograde aortic blood flow. Colour flow imaging showed a turbulent blood flow pattern across the aortic valve (fig 1). The diameter of the functional aortic valve orifice was approximately 6 mm based on the width of the colour jet. The aortic arch was normal. Repeat fetal echocardiograms at 34 and 35 weeks' gestation showed progressive right ventricular dilatation with no change in left ventricular dimensions.

Because of the echocardiographic evidence of poor left ventricular function it was decided that delivery should be by elective caesarean section once pulmonary maturity could be established. Serial amniocenteses were performed twice weekly until 36 weeks, when the amniotic fluid biochemical profile was consistent with fetal pulmonary maturity. Subsequently a male infant weighing 3390 g was delivered by caesarean section. The infant was vigorous at birth; however, within minutes he showed evidence of poor peripheral perfusion with symmetrically weak pulses. Considerable bradycardia and cyanosis developed shortly afterwards and he was intubated and ventilated and started on continuous infusions of prostagladin E1 (0 1 μg/kg/min) and dopamine (10 μg/kg/min).

Cross sectional echocardiography confirmed the

Requests for reprints to Dr Murray A Robertson, Division of Pediatric Cardiology, 2C300, Walter C Mackenzie Health Science Centre, Edmonton, Alberta, Canada T6G 2B7.

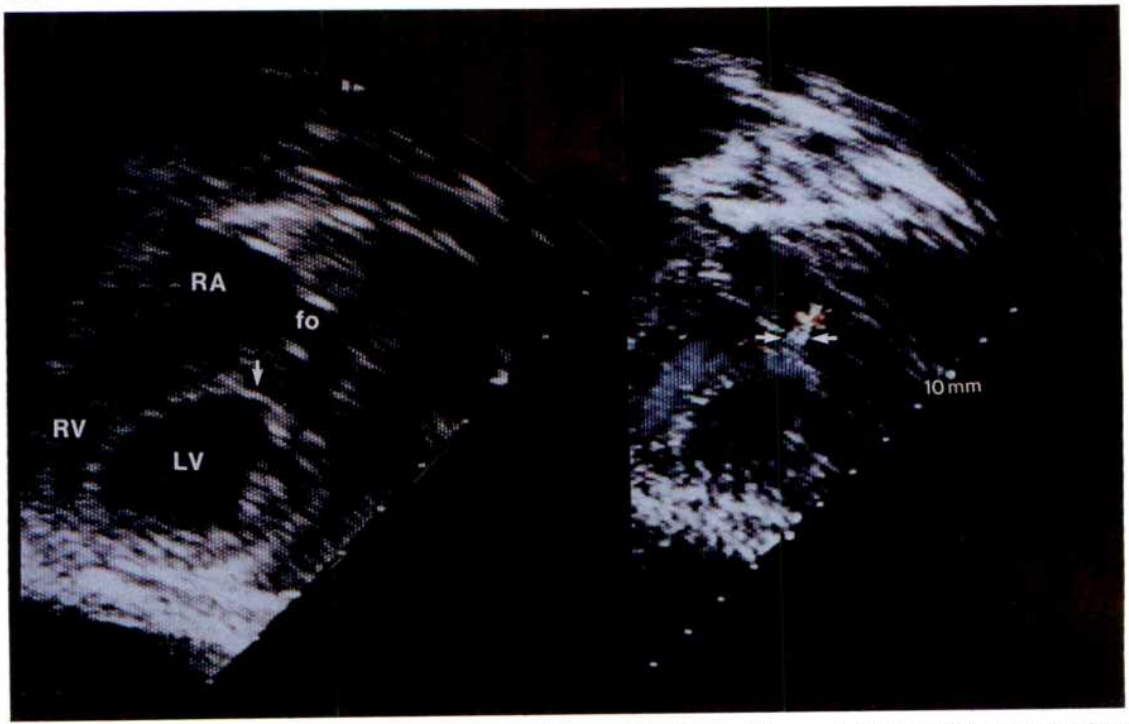


Figure (*Left*) *Cardiac four chamber view showing a dilated left ventricle. The vertical arrow indicates a thickened immobile aortic valve.* (*Right*) *Same view showing a pattern of turbulent blood flow across the aortic valve by colour Doppler. The effective diameter of the orifice is approximately 6 mm. RA, right atrium; RV, right ventricle; LV, left ventricle; fo, foramen ovale.*

diagnosis of aortic valve stenosis (annulus diameter 7 mm). The pressure gradient across the left ventricular outflow tract calculated by Doppler echocardiography was only 10 mm Hg, which was consistent with the poor left ventricular function and low cardiac output. The ductus arteriosus was patent with right to left systolic shunting and no aortic coarctation. At approximately two hours of age the infant underwent a surgical aortic valvotomy under inflow occlusion. The procedure was well tolerated and positive pressure ventilation and inotropic support was stopped by the third postoperative day. On the second postoperative day the Doppler derived pressure gradient across the aortic valve had increased to 25 mm Hg. This value is consistent with improved left ventricular function. There was trivial aortic valve regurgitation.

The infant was discharged home on the tenth postoperative day. At follow up at six months the child was symptom free and thriving. Echocardiography showed normal left ventricular dimensions and a shortening fraction of 43%. Doppler echocardiography showed a pressure gradient of 40 mm Hg across the aortic valve.

Discussion

There are few published data on the fetal diagnosis and subsequent perinatal management of congenital cardiac lesions. A recent case report described an infant in whom aortic valve stenosis had been previously diagnosed in utero who was delivered by caesarean section at 35 weeks' gestation because there had been prolonged rupture of membranes, maternal fever, and leucocytosis.[6] The prenatal diagnosis did not seem to influence the mode of delivery although the authors suggested that when there is left ventricular myocardial dysfunction delivery should be by caesarean section to avoid undue stress. We support this approach and suggest that when increasing myocardial dysfunction in utero has been shown the neonatal prognosis may be improved by early elective caesarean section once pulmonary maturity can be reasonably assured. These infants should be delivered in a tertiary care centre with expertise in neonatology, paediatric cardiology, and paediatric cardiac surgery. An elective caesarean section allows both the coordination of these specialists well in advance of delivery and the efficient postnatal management and stabilisation of the infant. Once the condition of the infant is stabilised and the prenatal diagnosis is confirmed by echocardiography, aortic valvotomy, may be performed.

The concept that early delivery may be beneficial in certain cardiac lesions associated with fetal myocardial dysfunction is controversial. Although not proven, we speculate that in the case of critical aortic valve stenosis intrauterine myocardial dysfunction is progressive. Presumably high left ventricular pressures with increased wall stress are not adequately compensated by increased myocardial blood flow. This may result in myocardial ischaemia which is possibly more severe in the subendocardium. In addition, left ventricular end diastolic compliance would theoretically decrease thereby impairing left ventricular filling which in turn increases right ventricular volumes. In this case we saw progressive right ventricular dilatation in utero. Early delivery and relief of the left ventricular outflow tract obstruction may prevent further myocardial dysfunction and enhance postnatal recovery of cardiac function. In this infant there was rapid recovery of left ventricular function after surgical aortic valvotomy; but it is not known whether recovery would have been rapid had the pregnancy been allowed to progress to term.

For most cardiac lesions there is no significant deterioration in cardiac function in utero and therefore early delivery is not indicated. However, fetuses with cardiac lesions such as critical aortic valve stenosis with evidence of intrauterine myocardial dysfunction may benefit from early delivery and treatment. By adopting a coordinated, perinatal approach as outlined here we feel that the morbidity and mortality associated with neonatal critical aortic valve stenosis may be reduced. But a larger number of patients will have to be treated before any conclusions can be reached.

References

1 Duncan K, Sullivan I, Robinson P, Horvath P, deLaval M, Stark J. Transventricular aortic valvotomy for critical aortic stenosis in infants. *J Thorac Cardiovasc Surg* 1987;**93**:546–50.

2 Dobell ARC, Bloss RS, Gibbons JE, Collins GF. Congenital valvular aortic stenosis: surgical management and long-term results. *J Thorac Cardiovasc Surg* 1981;**81**:916–20.

3 Allan LD, Tynan M, Campbell S, Anderson RH. Identification of congenital cardiac malformations by echocardiography in midtrimester fetus. *Br Heart J* 1981;**46**:358–62.

4 Kleinman CS, Donnerstein RL. Ultrasound assessment of cardiac function in the intact human fetus. *J Am Coll Cardiol* 1985;**5**:845–945.

5 St John Sutton MG, Gewitz MH, Shah B, *et al.* Quantitative assessment of growth and function of the cardiac chambers in the normal human fetus: a prospective longitudinal echocardiographic study. *Circulation* 1984;**69**:645–54.

6 Huhta JG, Carpenter RJ, Moise KJ, Deter RL, Ott DA, McNamara DG. Prenatal diagnosis and postnatal management of critical aortic stenosis. *Circulation* 1987;**75**:573–6.

Br Heart J 1989;61:368–71

Wolff-Parkinson-White syndrome after transplantation of the heart

J-J GOY,* L KAPPENBERGER,* M TURINA†

*From the *Division of Cardiology, Department of Medicine, University Hospital, Lausanne; and †Department of Cardiovascular Surgery, University Hospital, Zürich, Switzerland*

SUMMARY The classic features of Wolff-Parkinson-White syndrome developed in a 49 year old man after he was given the heart of a donor who had had a normal electrocardiogram. The recipient showed type A pre-excitation on the surface electrocardiogram and clinically important paroxysmal supraventricular tachycardia. An electrophysiological study showed a left sided accessory pathway and dissociation between donor and recipient atrial activity during tachycardia. The arrhythmia was controlled by flecainide.

The suitability of heart donors is based on clinical examination, electrocardiogram, chest *x* ray, and echocardiogram.[1] A careful history taken from a member of the donor's family will help to assess the likelihood of a cardiovascular abnormality that might not be detected by these tests. We report the case of a patient who was given the heart of a symptomless donor who had had a normal electrocardiogram. The recipient subsequently presented with Wolff-Parkinson-White syndrome.

Case report

In September 1986, a 49 year old white man was accepted for heart transplantation. He had severe dilated cardiomyopathy caused by ischaemic heart disease and was in severe heart failure (New York Heart Association class IV). Heart transplantation was performed at the University Hospital of Zurich on 2 February 1987. The donor, a white man aged 19, had irreversible severe cerebral damage after a car accident. The donor did not have a history of cardiovascular disease and according to relatives had never had palpitations. His electrocardiogram showed non-specific ST segment changes, without any signs of pre-excitation (fig 1a); the chest *x* ray and echocardiogram were within normal limits. Heart transplantation was performed and the patient was extubated on the second postoperative day. The immediate postoperative electrocardiogram showed normal sinus rhythm with sinus tachycardia and non-specific ST segment modification. On day 7 he had an infection caused by *Pseudomonas aeruginosa;* this was successfully treated with antibiotics. The patient was maintained on azathioprine 100 mg/daily and cyclosporin 220 mg/daily.

When he first attended as an outpatient for myocardial biopsy he complained of two or three episodes of dizziness that had coincided with a rapid heart rate. The clinical examination was normal apart from a high blood pressure of 170/110 mm Hg. The electrocardiogram surprisingly showed typical patterns of Wolff-Parkinson-White syndrome (PR interval 80 ms) (type A) with a delta wave axis that was compatible with a left sided accessory pathway (fig 1b).

An electrophysiological investigation was performed. The atrioventricular conduction intervals were normal, as were effective refractory periods of the atrioventricular node and atrium (AH = 90 ms, HV = 50 ms, H-delta = 10 ms). Orthodromic tachycardia (cycle length 300 ms) was easily induced by two atrial extrasystoles. The refractory period of the accessory pathway was 380 ms for anterograde conduction and 260 ms for retrograde conduction. During tachycardia the earliest atrial electrocardiogram was recorded in the distal coronary sinus, confirming the left sided site of the accessory pathway. In sinus rhythm and during tachycardia (fig 2a), two atrial depolarisations could be seen (A1 and A2). A1 represents the depolarisation of the remaining part of the recipient atrium and A2 is the depolarisation of the donor atrium.

During the tachycardia, the atrium of the donor

Requests for reprints to Dr J-J Goy, Division of Cardiology, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland.

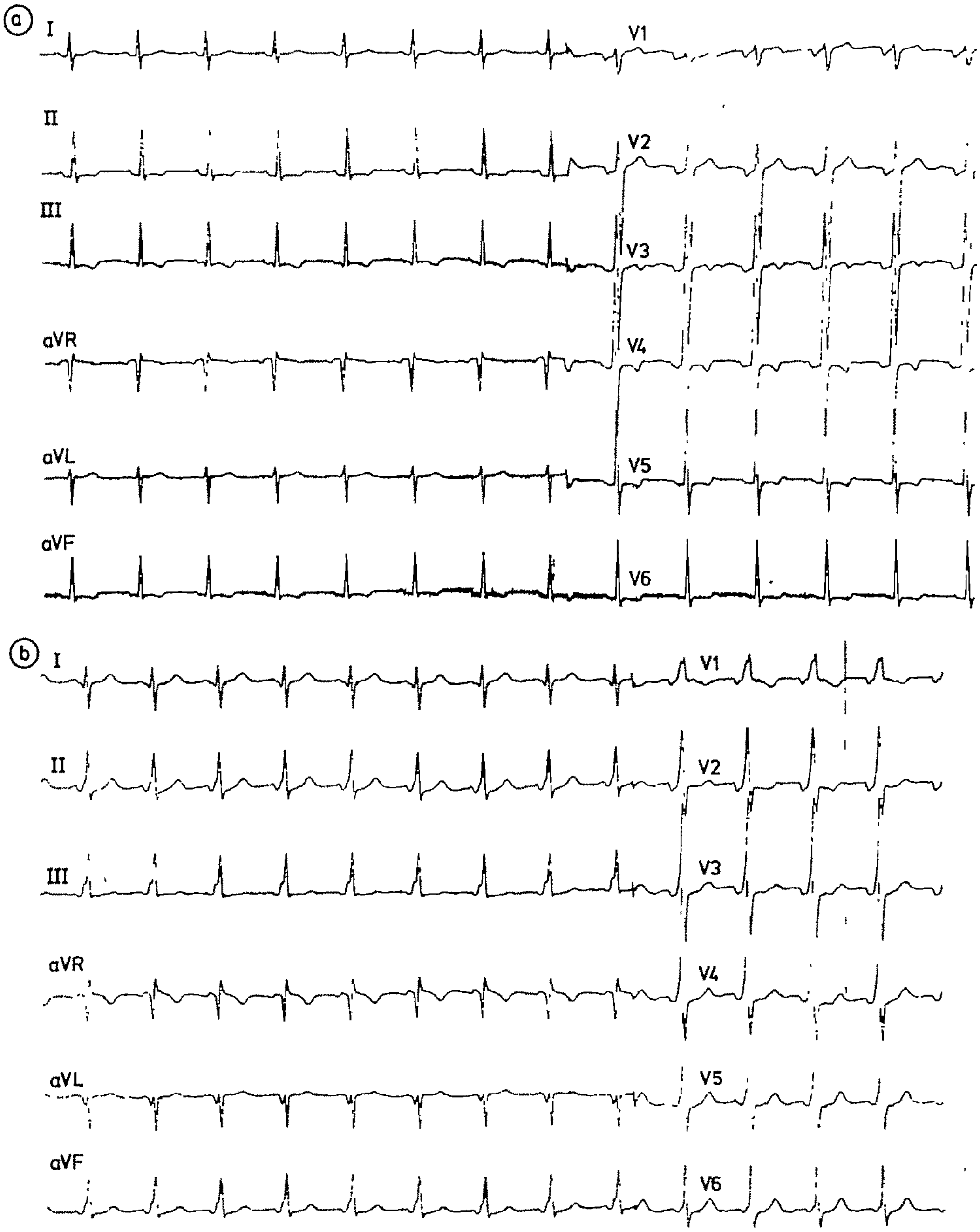


Fig 1 *(a) Twelve lead electrocardiogram recorded in the donor (b) Twelve lead electrocardiogram showing the typical patterns of Wolff-Parkinson-White syndrome.*

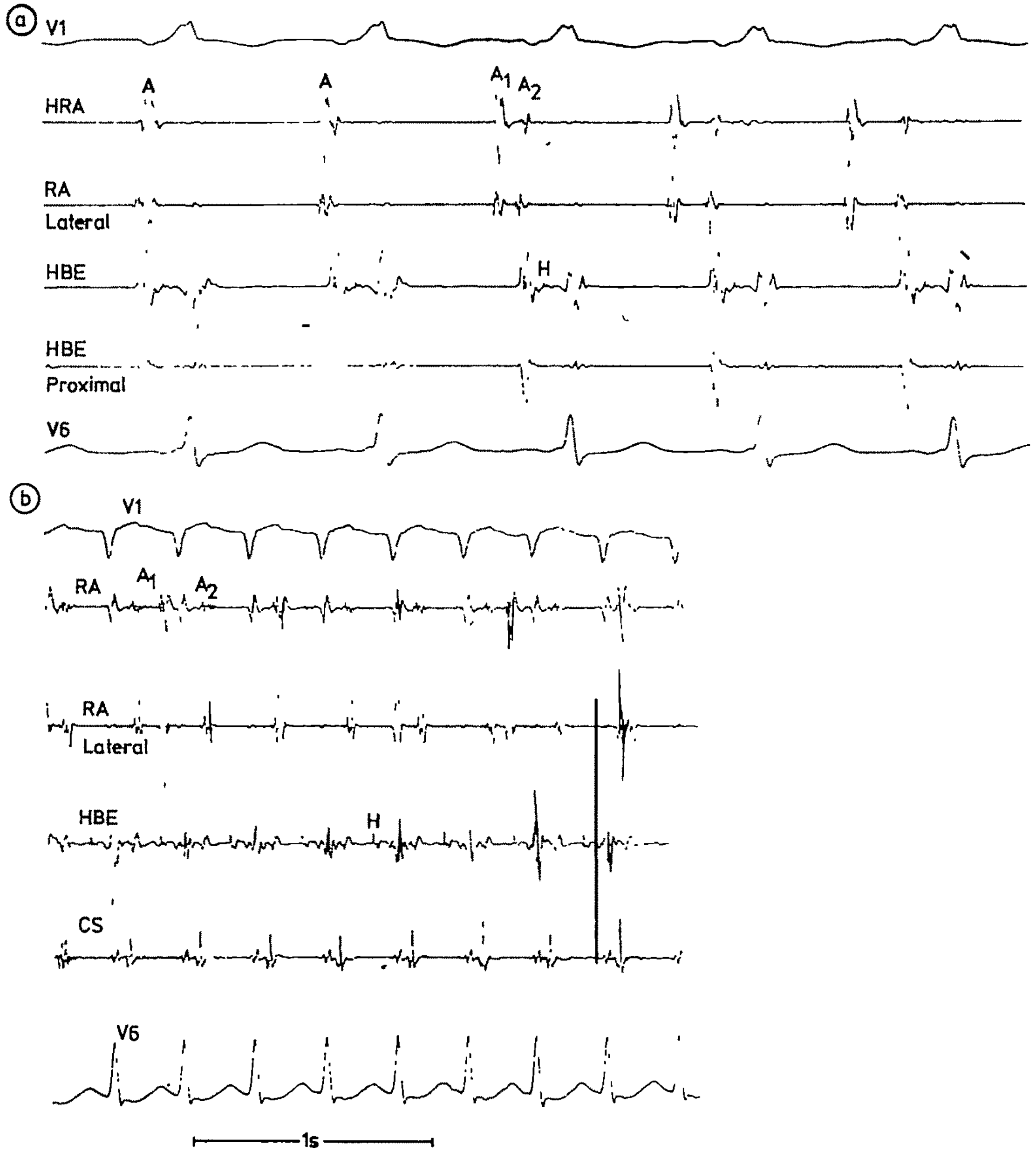


Fig 2 *(a) Endocavitary electrocardiogram showing two different atrial depolarisations, A1 and A2. A1 is the signal of the recipient atrium and A2 is the depolarisation of the donor atrium. HRA, high right atrium electrocardiogram, HBE, His bundle electrocardiogram. (b) Endocavitary electrocardiogram during orthodromic reentrant tachycardia. A1 (recipient atrium) was not part of the circuit A2 (donor atrium) and was retrogradely activated. The earliest site of retrograde activation was in the coronary sinus. RA, high right atrium electrocardiogram; HBE, His bundle electrocardiogram, CS, coronary sinus.*

heart was involved in the reentry circuit, while the recipient heart remained in normal sinus rhythm with sinus tachycardia (fig 2b). Episodes of tachycardia were poorly tolerated and required conversion to sinus rhythm after 30 to 60 seconds with programmed atrial stimulation. Atrial fibrillation was not induced. Amiodarone 600 mg/daily was prescribed, but was stopped a month later when tachycardia recurred and there were side effects. The patient was successfully treated with flecainide (100 mg twice a day), which controlled the symptoms and suppressed episodes of spontaneous paroxysmal tachycardia.

Discussion

As the number of heart transplants increases donor-transmitted cardiac disease, although rare, is likely to occur. Wolff-Parkinson-White syndrome is found in 0·1–0·2% of the general population,[2] and this case emphasises the need for taking a thorough history of the donor and to have several recent and, if possible, earlier electrocardiograms. If doubt persists about the presence of an accessory pathway, limited atrial and ventricular stimulation should be performed before removal of the heart.

Patients with accessory pathways should not be considered as heart donors, even if they do not have a history of palpitation. Supraventricular tachycardia may be incapacitating or dangerous to the recipient. Moreover, as this case shows, tachycardia and evidence of accessory pathways may become apparent only after transplantation. The explanation of this phenomenon remains unclear. It is theoretically possible that conducting pathways might develop between the donor and recipient atria, and might form the basis of a reentry circuit. However, in our patient the dissociated activity in the recipient atria rules out this possibility. A further possibility is that intermittent pre-excitation might be present in the donor heart—this phenomenon is well known in the Wolff-Parkinson-White syndrome especially with left sided accessory pathways.[3] The location and the relatively long anterograde refractory period may explain the absence of pre-excitation in the donor heart. After transplantation vagal control was lost but the response to sympathetic nervous stimuli persisted, resulting in shortening of the refractory periods of the accessory pathway.[4] Thus pre-excitation occurred and orthodromic reciprocating tachycardia could be initiated.

References

1 Davis FD. Coordination of cardiac transplantation: patient processing and donor organ procurement. *Circulation* 1987;75:29–39.

2 Vidaillet HJ, Pressley JC, Henke E, Harrell FE, German LD. Familial occurrence of accessory atrioventricular pathways (preexcitation syndrome). *N Engl J Med* 1987;**317**:65–9.

3 Sung RJ, Toi DY. Electrophysiologic characteristics of accessory connections; an overview. In: Benditt DG, Benson DW, eds. *Preexcitation syndrome*. Boston: Martinus Nijhoff, 1986:165–99.

4 Wellens HJJ, Brugada P, Roy D, Weiss J, Bär FW. Effect of isoproterenol on the anterograde refractory period of the accessory pathway in patients with the Wolff Parkinson White syndrome. *Am J Cardiol* 1982;**50**:180–4.

Br Heart J 1989;**61**:372–4

Serial angiographic findings during the development of a saccular aneurysm of the coronary artery in association with unstable angina

JOHN GOUDEVENOS, MARTIN BEEN, DAVID WILLIAMS

From the Cardiothoracic Centre, Freeman Road Hospital, Newcastle upon Tyne

SUMMARY A 60 year old man presented with unstable angina and electrocardiographic features suggestive of disease of the left anterior descending coronary artery. Angiography showed slight proximal narrowing in this artery with reduced density of contrast that suggested an associated thrombus. Repeat angiography after 24 hours of heparin administration showed the development of a small saccular aneurysm. Three weeks later, after a further episode of unstable angina, angiography showed enlargement of the aneurysm. Although there were no further episodes of angina, repeat angiography three months after the initial event showed further slight enlargement of the aneurysm.

It is suggested that the episodes of angina at rest were secondary to embolisation of thrombotic or atheromatous material or both.

The finding of single or multiple aneurysmal dilatations of coronary arteries is fairly common in patients with ischaemic heart disease[1] and is usually referred to as coronary ectasia. Isolated saccular aneurysms are much less common,[2] although the recent report of similar findings in a small number of patients after percutaneous transluminal coronary angioplasty[3] suggests that in future the incidence may increase.

There has been speculation about the pathophysiological development of the more common coronary aneurysms[4 5] but the opportunities for serial angiographic studies have been limited. Despite the increase in early angiographic studies in unstable angina, there are few opportunities for serial angiographic study because mechanical intervention by percutaneous transluminal coronary angioplasty or operation often follows.

The time course, associated symptoms, and serial angiographic findings in a patient with unstable angina in whom a saccular coronary aneurysm developed without any mechanical intervention are therefore of interest.

Case report

A 60 year old man with a previous inferior myocardial infarction presented with a typical history of recent onset exertional angina culminating in episodic rest pain. He was monitored in the coronary care unit and an oral calcium antagonist, aspirin, and a β blocker were added to his nitrate treatment. The admission electrocardiogram showed evidence of his old inferior infarct but there were no acute changes.

Despite bed rest and medical treatment he continued to have episodic pain associated with T wave inversion in leads V2–V6 but with no increase in the activity of cardiac enzymes. Coronary angiography performed by the Judkins technique showed extensive disease of the right coronary artery but the left anterior descending artery, suspected to be the ischaemia related vessel, had a proximal stenosis of < 50% of the luminal diameter. There was some reduction in the density of contrast in the proximal left anterior descending artery, suggesting the presence of thrombus adjacent to the mild lesion. Heparin was started and the femoral sheath was left in situ. Repeat angiography at 24 hours showed some increase in contrast density in the proximal left anterior descending artery and the development of a small saccular aneurysm.

No further episodes of myocardial ischaemia occurred, the T waves returned towards normal, and before hospital discharge he performed a graded treadmill exercise test. He completed five minutes and 45 seconds of a standard Bruce protocol, and he

Requests for reprints to Dr Martin Been, Department of Cardiology, Freeman Road Hospital, Freeman Road, Newcastle upon Tyne NE7 7DN.

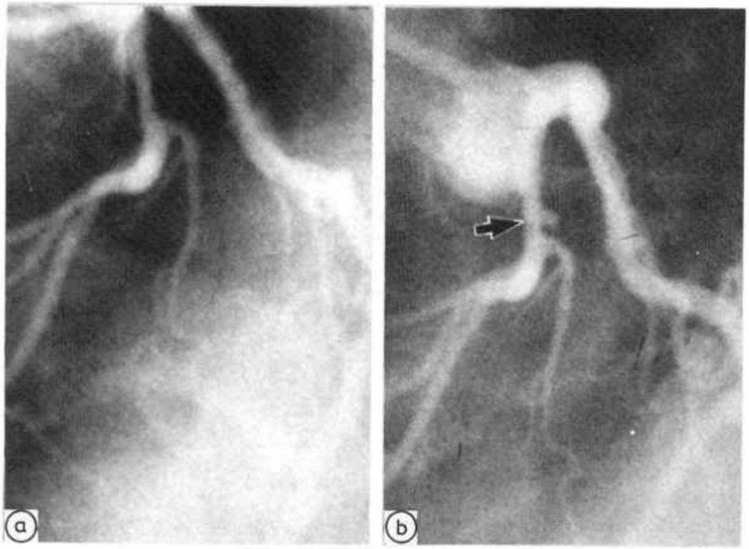


Figure *(a) Left anterior oblique projection with cranial tilt showing reduced density of contrast in the proximal left anterior descending artery associated with slight narrowing of this segment. (b) Repeat coronary angiogram three months later showing further enlargement of the aneurysm. The proximal coronary artery appears to be only slightly stenosed.*

stopped because of dyspnoea. At peak exercise there was 2 mm ST depression in lead V5. He was discharged on the above medication with the addition of warfarin.

Three weeks later he attended for a radionuclide gated blood pool scan, which showed good left ventricular function with an overall ejection fraction of 41%. He had been free of further angina until the morning of his scan when he was woken by ischaemic pain and developed further rest pain before leaving home. He was readmitted to the coronary care unit and later that day had a further episode of rest pain associated with ST elevation of 1·5 mm in leads V2 and V3. He responded symptomatically to glyceryl trinitrate but was left with mild residual ST depression and T wave inversion in leads V2–V5. Repeat angiography showed enlargement of the saccular aneurysm with some progression in severity of the proximal coronary stenosis and no convincing evidence of coronary thrombus.

No further clinical events occurred but repeat exercise testing showed evidence of symptom free ischaemia. He completed eight minutes of an identical Bruce protocol and significant ST depression developed in lead V5 by four minutes. Anticoagulants were stopped but other antianginal medication continued.

In view of the exercise test findings and uncertainty as to the development of the aneurysm, a further angiogram was performed three months after the original admission. No further episodes of angina had occurred since his previous hospital admission. Contrast angiography showed that left ventricular function remained good. Coronary angiography showed that there had been some further enlargement of the aneurysm (figure) but there was only slight narrowing of the proximal left anterior descending artery.

Discussion

Aneurysms are described as fusiform when they are spindle shaped and as saccular when the pouch has a narrow neck.[6] In some reports fusiform coronary aneurysms have been labelled as saccular when they assume a globular configuration even though a narrow neck is not present.[4] Fusiform dilatation or "coronary ectasia" is a relatively common finding, which is usually present in conjunction with atherosclerotic narrowings; the pathogenesis of such aneurysmal dilatation is thought to involve intimal disruption or to be secondary to medial disease.[4 5] In contrast, true saccular coronary artery aneurysms are uncommon and little is known of their pathogenesis or course. The appearance of the aneurysm in this case differs from that in most large reviews of coronary aneurysms because they included cases of coronary ectasia.[1 4] The angiographic appearance of coronary aneurysms at the site of angioplasty seems to be similar to what we found in our case.[3] The availability of serial angiograms during the development of the aneurysm has allowed us to link the anatomical changes with the associated clinical events.

The close association between unstable angina, myocardial infarction, intimal tears, and thrombus formation has become increasingly recognised. However, our case has several unusual features. The initial angiographic appearance was of a stenosis of < 50% of the luminal diameter of the proximal left anterior descending artery —an unexpected finding in a patient with unstable angina—and anterior ST changes during rest pain. Reduced density of contrast at the site of the lesion at that time suggested the presence of thrombus. The initial episodes of pain may have been caused by further local thrombus formation giving rise to a transient increase in obstruction to flow or caused by embolisation of thrombotic or atheromatous material. Embolisation seems more likely to be the mechanism of myocardial ischaemia in this case because the electrocardiographic changes persisted for days despite wide patency of the left anterior descending artery.

Embolisation of material may produce ischaemia or have more serious consequences. Platelet and fibrin microthrombi were quite common in ischaemic heart disease and in particular may be important in sudden cardiac death in young people.[7]

Heparin infusion would have been expected to reduce the amount of thrombus present. It is conceivable that in so doing the underlying ulcerated plaque was exposed, thus revealing the small protrusion of contrast seen on the second angiogram. The fact that the aneurysm became larger in association with further unstable angina again suggests the possibility of embolisation, perhaps of the contents of the plaque or of thrombotic material formed within it. Such mechanisms have been postulated to explain the development of coronary artery aneurysms[5] but no serial angiographic studies have been reported. The likelihood of embolisation of atheromatous material as an integral part of the sequence has also been suggested as the explanation for the finding of a high incidence of reduced left ventricular function in patients with coronary aneurysms in the absence of coronary occlusion. In our patient left ventricular function was well maintained.

The role of anticoagulants, antiplatelet treatment, or operation is uncertain, but operation has been suggested as a means of reducing emboli and removing the risk of rupture. In the absence of current symptoms and the very low incidence of atherosclerotic coronary artery rupture we elected to continue medical treatment.

References

1 Robinson FC. Aneurysms of the coronary arteries. *Am Heart J* 1985;**109**:129–35.

2 Anabatwi IN, de Leon JA. Arteriosclerotic aneurysms of the coronary arteries. *J Thorac Cardiovasc Surg* 1974;**68**:226–8.

3 Hill JA, Margolis JR, Feldman RL, Conti CR, Pepine CJ. Coronary arterial aneurysm formation after balloon angioplasty. *Am J Cardiol* 1983;**52**:261–4.

4 Befeler B, Aranda JM, Embi A, Mullin FL, El-Sherif N, Lazzara R. Coronary artery aneurysms; study of their etiology, clinical course and effect on left ventricular function and prognosis. *Am J Med* 1977; **62**:597–607.

5 Berkoff HA, Rowe GG. Atherosclerotic ulcerative disease and associated aneurysms of the coronary arteries. *Am Heart J* 1975;**90**:153–7.

6 Lindsay J Jr. Diseases of the aorta and vena cavae. In. Hurst JW, ed. *The heart*. 4th ed. New York: McGraw-Hill, 1978:1849–56.

7 El-Maraghi N, Genton E The relevance of platelet and fibrin thromboembolism of the coronary microcirculation, with special reference to sudden cardiac death. *Circulation* 1980;**62**:936–44.

Br Heart J 1989;**61**:375–7

Unruptured aneurysm of the sinus of Valsalva presenting with isolated heart block: echocardiographic diagnosis and successful surgical repair

R A S AHMAD, S STURMAN,* R D S WATSON

*From the Departments of Cardiology and *Medicine, Dudley Road Hospital, Birmingham*

SUMMARY A 31 year old man presented with intermittent dizziness and electrocardiographic evidence of a severe conduction disturbance, with asystolic pauses of up to six seconds, and was treated by implantation of a permanent pacemaker. Echocardiography showed an enlarging aneurysm of the right sinus of Valsalva extending into the interventricular septum. This was confirmed by aortography, and successful surgical repair was carried out. The characteristic diastolic expansion of the aneurysm and the demonstration of continuity between the septal extension and the related aortic sinus were useful diagnostic features.

Aneurysmal dilatation and progressive enlargement of one of the sinuses of Valsalva, most often the right coronary sinus, normally goes undetected during life until rupture occurs. Rarely, the aneurysm presents with evidence of obstruction of the right ventricular outflow tract, aortic insufficiency, conduction abnormalities, or coronary artery compression in the absence of rupture.[1] We report a patient who had a severe conduction disorder caused by extension of a congenital aneurysm into the interventricular septum and describe the echocardiographic features.

Case report

A 31 year old Pakistani man was admitted with a short history of intermittent vague dizziness associated with palpitation, near syncope, cold extremities, and mild dyspnoea. There was no history of recent chest pain or injury. On examination his pulse was normal with a regular rhythm at a rate of 70 beats/min, but with intermittent pronounced bradycardia. There were multiple, healed punched out ulcers on both shins. Examination of the fundi showed extensive bilateral retinal scarring with appearance of healed choroidoretinitis. Examination was otherwise unremarkable.

His electrocardiogram showed sinus rhythm, a normal PR interval, right bundle branch block, and left anterior hemiblock. A chest radiograph was normal. Laboratory investigations showed normal blood count, erythrocyte sedimentation rate, serum electrolytes, and renal and liver function tests. Electrocardiographic monitoring showed symptomatic episodes of complete atrioventricular block with ventricular standstill lasting up to six seconds; a temporary transvenous pacemaker was inserted. Two days later a permanent VVI pacemaker was implanted, programmed to a rate of 50 beats/min.

Because he was young an echocardiographic examination was carried out, primarily to exclude heart muscle disease. This showed an echo free space high within the interventricular septum (fig 1) which appeared, on cross sectional examination, as a cystic mass near the left ventricular outflow tract. The appearances of the aortic and mitral valves, cardiac chambers, and aortic root were otherwise normal.

Further investigations were carried out because of the "cyst" in the ventricular septum seen on echocardiography and the cutaneous and retinal changes. There was no evidence of tuberculous infection. Blood cultures were sterile. Serological tests for syphilis, toxoplasma, and hydatid antibodies, and rheumatoid and antinuclear factors were negative. A Kveim skin test was negative.

One week later his conduction disturbance progressed to persistent complete atrioventricular block. Repeat echocardiography showed enlargement of the cyst in the septum and the characteristic

Requests for reprints to Dr R A S Ahmad, Department of Cardiology, Dudley Road Hospital, Dudley Road, Birmingham, B18 7QH

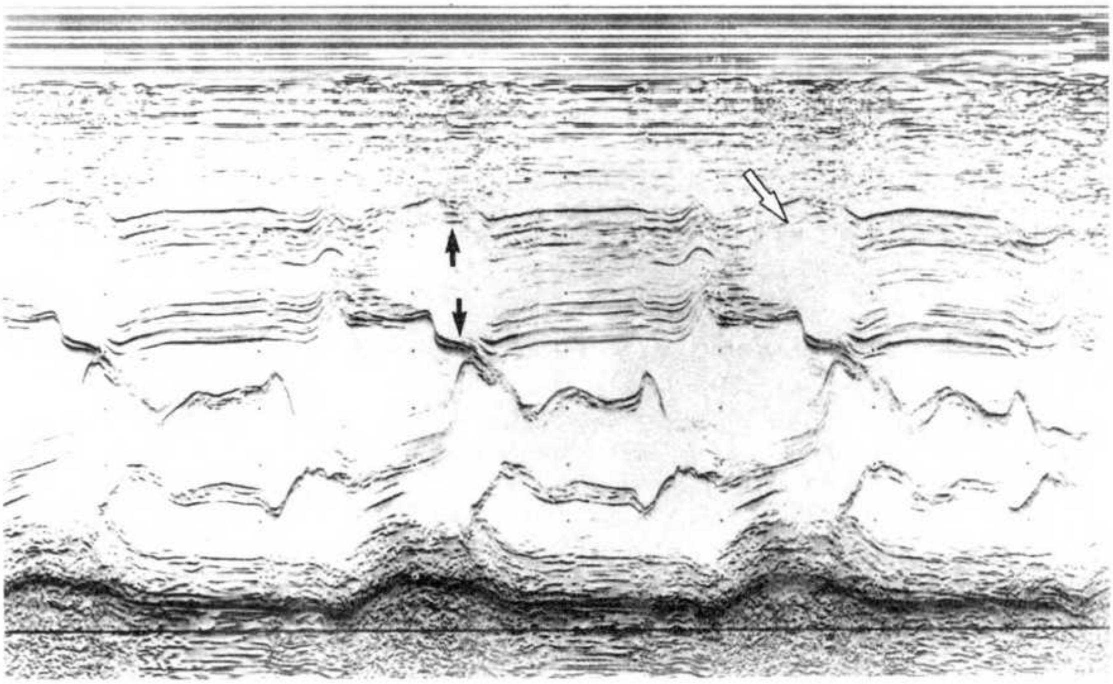


Fig 1 *M mode echocardiogram showing the large echo free space (large arrow) within the grossly thickened interventricular septum. Expansion of the aneurysm during early diastole (small arrows) can be clearly seen, coinciding with maximum separation of the mitral valve leaflets.*

appearances of an unruptured aneurysm of the sinus of Valsalva, as previously reported.[2 3] Diastolic expansion and systolic "emptying" were apparent particularly in the long axis parasternal view. The echo free space extended rostrally, becoming continuous with the aortic root at the level of the right sinus of Valsalva.

The aneurysm did not appear to impinge appreciably on to the left or right ventricular outflow tracts. A root aortogram (fig 2) confirmed the presence of an unruptured aneurysm of the right coronary sinus extending into the interventricular septum. There was no evidence of aortic incompetence. Coronary angiography showed no abnormality.

In view of the progressive nature of the lesion we referred the patient for surgical repair five months after his initial presentation.

OPERATIVE FINDINGS

The heart was normal in size. Through the right ventricular free wall a mass could be felt in the upper part of the interventricular septum. The ascending aorta was normal and was opened under cardiopulmonary bypass. The entrance of the aneurysm, below the origin of the right coronary artery, measured approximately 1 cm in diameter. The right coronary cusp of the aortic valve was slightly distorted. The other two cusps and sinuses appeared normal. The aneurysm extended into the interventricular septum, bulging into the right ventricle and to a lesser extent into the left ventricular outflow tract. The opening of the aneurysm was closed with a Dacron patch and any distortion of the aortic valve was avoided. There was no intraoperative evidence of important aortic incompetence.

His subsequent course was uncomplicated. He remained in complete atrioventricular block and was left with a ventricular demand pacemaker. At follow up three months later he was symptom free with only an insignificant early diastolic murmur. Repeat echocardiography showed disappearance of the echo free space within the interventricular septum. The thickness of the septum had returned to normal.

Discussion

A congenital aneurysm of a single sinus of Valsalva is an uncommon anomaly attributed to deficiency or absence of media in the aortic wall behind the sinus.[1] Enlargement of the aneurysm may occur and result in rupture, usually during the third or fourth decades of life. Over 90% of congenital aneurysms affect the

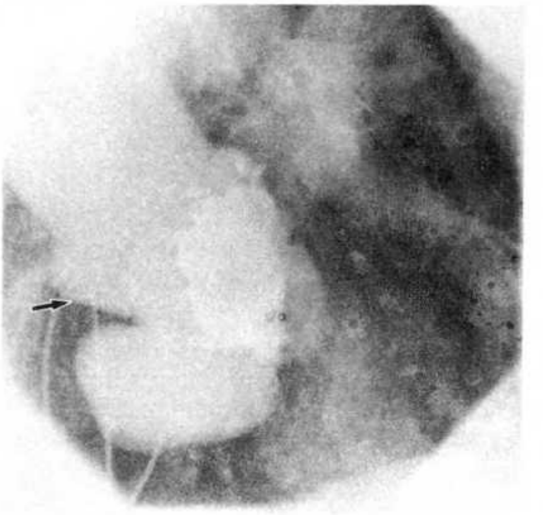


Fig 2 *Root aortogram in left anterior oblique projection showing a normal left coronary sinus and the intact aneurysm of the right coronary sinus extending into the interventricular septum.*

right or non-coronary sinuses and normally protrude, or rupture, into the right ventricle or right atrium.[1] Rupture, most often in a young male patient, presents with chest pain, heart failure, or a loud continuous murmur. Extension of an aneurysm of a sinus of Valsalva into the interventricular septum to produce symptomatic conduction disturbance is very rare. Acquired aneurysms are mainly attributed to syphilis, infective endocarditis, or tuberculosis. In the absence of a clear cause a congenital aetiology is assumed.

The diagnosis has been made before rupture in patients presenting with aortic incompetence, bacterial endocarditis, or signs of obstruction of the right ventricular outflow tract with or without congestive cardiac failure.[1-3]

Echocardiography is useful in the diagnosis of ruptured aneurysms of the sinus of Valsalva[4] and the diagnosis and follow up of unruptured aneurysms complicated by obstruction of the right ventricular outflow tract or infective endocarditis.[2 5 6] Lewis and Agathangelou reported the echocardiographic diagnosis of an unruptured aneurysm of the right sinus of Valsalva in a patient with aortic regurgitation, infective endocarditis, and electrocardiographic evidence of bifascicular block.[2] They commented on the value of demonstrating the continuity between the echo free space within the upper septum and the aortic root at the level of the right coronary sinus, which differentiates the condition from an aneurysm of the ventricular septum. Hands *et al* described the echocardiographic appearances of an unruptured aneurysm of the right coronary sinus with extension into the interventricular septum and the characteristic systolic "emptying" and diastolic expansion into the left ventricular outflow tract.[3] This patient developed right bundle branch block and severe aortic incompetence requiring valve replacement.

In our patient the echocardiographic diagnosis was made by serendipity. There were no clinical features of aortic valve or aortic root abnormality and the echocardiogram was carried out to exclude heart muscle disease.

The course of unruptured congenital aneurysms is unknown. Survival for 19 years without operation was reported in a patient with a congenital aneurysm of the left sinus of Valsalva.[7] There are no other reports of long term survival without operation. In our patient the rapid progression of the conduction disorder and increase in size of the septal extension prompted us to refer him for operation.

We thank Mr R Norton, consultant cardiothoracic surgeon, Walsgrave Hospital, Coventry, who operated on this patient and Dr G D Beevers, Reader in Medicine and honorary consultant physician, Dudley Road Hospital who shared his care.

References

1 Fishbein MC, Obma R, Roberts WC. Unruptured sinus of Valsalva aneurysm. *Am J Cardiol* 1975; **35**:918–22.

2 Lewis BS, Agathangelou NE. Echocardiographic diagnosis of unruptured sinus of Valsalva aneurysm. *Am Heart J* 1984;**107**:1025–7.

3 Hands ME, Lloyd BL, Hung J. Cross-sectional echocardiographic diagnosis of unruptured right sinus of Valsalva aneurysm dissecting into the interventricular septum. *Int J Cardiol* 1985;**9**:380–3.

4 Engel PJ, Held JS, van der Bel-Kahn J, Spitz H. Echocardiographic diagnosis of congenital sinus of Valsalva aneurysm with dissection of the interventricular septum. *Circulation* 1981;**63**:705–11.

5 Faillace RT, Greenland P, Nanda NC. Rapid expansion of a saccular aneurysm on the left coronary sinus of Valsalva: a role for early surgical repair? *Br Heart J* 1985;**54**:442–4.

6 Kiefaber RW, Tabakin BS, Coffin LH, Gibson TC. Unruptured sinus of Valsalva aneurysm with right ventricular outflow obstruction diagnosed by two-dimensional and Doppler echocardiography. *J Am Coll Cardiol* 1986;**7**:438–42.

7 Martin LW, Hsu I, Schwartz H, Wasserman AG. Congenital aneurysm of the left sinus of Valsalva. Report of a patient with 19-year survival without surgery. *Chest* 1986;**90**:143–5.

Br Heart J 1989;61:378–9

Propranolol induced bradycardia in tetralogy of Fallot

DEBORAH J CLARK, K C CHAN, JOHN L GIBBS

From the Department of Paediatric Cardiology, Killingbeck Hospital, Leeds

SUMMARY When an 18 month old girl who had tetralogy of Fallot and episodes of severe cyanosis with loss of consciousness was treated with propranolol there was some improvement. But when the dose was increased she had further episodes of near syncope. Holter monitoring showed extreme intermittent bradycardia with pauses of up to 2·6 seconds. The episodes of near syncope and the bradycardia resolved after propranolol was stopped.

Apparent failure of propranolol treatment may on rare occasions be related to drug induced bradycardia rather than to continued episodes of severe cyanosis.

Propranolol is widely accepted as an effective palliation for tetralogy of Fallot complicated by episodes of severe cyanosis.[1] Side effects of propranolol, such as bradycardia, congestive heart failure, bronchospasm, and hypoglycaemia, are well recognised in adults but seem to be rare in infancy even at high doses.[2] We report the case of a child with tetralogy of Fallot who was treated with propranolol and in whom continued episodes of pallor and near syncope seemed to be caused by propranolol induced bradycardia.

Case report

An 18 month old Asian girl with tetralogy of Fallot had typical episodes of severe cyanosis during which she became distressed and then limp. Sometimes she lost consciousness for up to 10 minutes. She weighed 8 kg and she was treated with propranolol 5 mg three times a day. This seemed to abolish the attacks. During a subsequent outpatient visit, however, she had a prolonged episode of severe cyanosis and lost consciousness. She was admitted to hospital and the dose of propranolol was increased to 8 mg three times a day. After this she had several episodes each day when she became pale and suffered near syncope. Unlike her usual episodes these attacks were not associated with preceding cyanosis or distress. Because she had intermittent sinus bradycardia during a 12 lead electrocardiogram, 24 hour Holter monitoring was performed and β blockade was not increased. She remained symptom free during the period of monitoring. Analysis of the recording showed sinus rhythm at a resting rate of 120 beats/minute with repeated daytime episodes of sinus bradycardia and sinus arrest resulting in extreme junctional bradycardia and pauses lasting up to 2·6 seconds (figure), followed by a slow junctional escape rhythm and recovery of normal sinus rhythm. The dose of propranolol was stopped and the child was sedated and nursed in a quiet room. After β blockade was stopped no further bradycardias occurred on continuous electrocardiographic monitoring and she remained free from episodes of severe cyanosis until she underwent corrective operation one week later. Her postoperative course was complicated by low cardiac output and she died three days after operation.

Discussion

Episodes of severe cyanosis may present with floppiness and pallor, transient vacant episodes, or convulsions.[3] Although the exact mechanism of these episodes is uncertain, treatment with propranolol often abolishes them.[4 5] Toxic effects are rare with the commonly used daily doses of between 2 and 5 mg/kg and doses of up to 14 mg/kg have proved both effective and free from side effects in children with supraventricular tachycardia.[2] Complications of treatment such as bradycardia, congestive heart failure, and somnolence have been reported in children, but these were rarely severe enough for treatment to be stopped.[6] The paroxysmal sinus arrest

Requests for reprints to Dr John L Gibbs, Department of Paediatric Cardiology, Killingbeck Hospital, York Road, Leeds LS14 6UQ

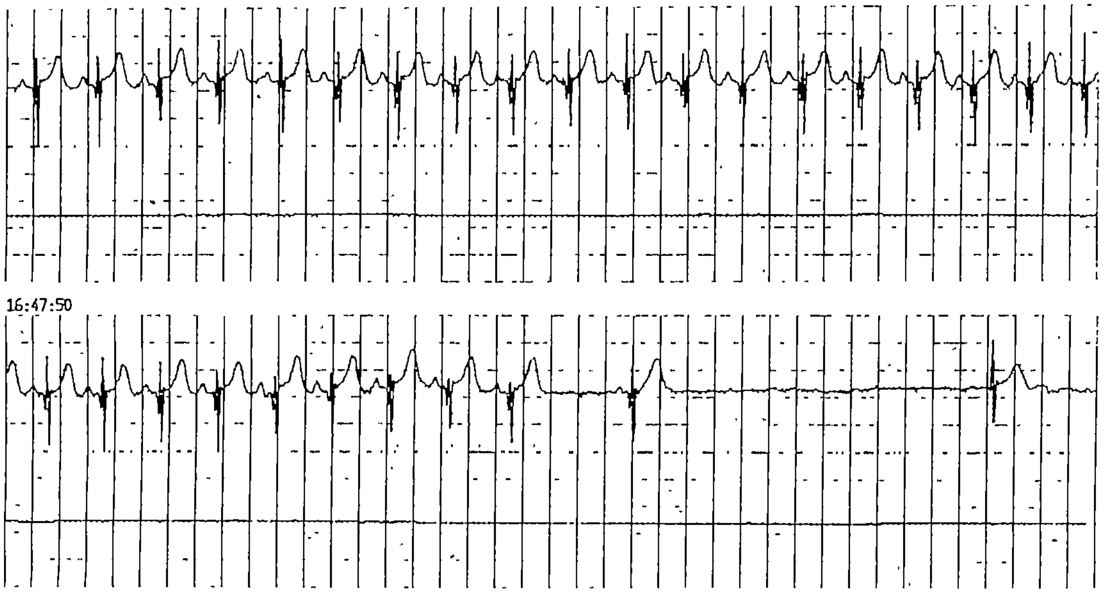


Figure *Part of the Holter monitor recording taken during treatment with propranolol 3 mg/kg a day, showing abrupt sinus bradycardia followed by sinus arrest and a junctional escape beat after a pause of 2·6 seconds.*

with episodes of extreme bradycardia that we saw in our patient has not been recognised before in a child treated with propranolol, irrespective of the dose given or the underlying cardiac abnormality.

Inadequate dosage may well be the most common cause of failure of episodes of severe cyanosis to respond to propranolol; an initial daily dose of 1 mg/kg has been suggested, gradually increased up to a maximum of 5 mg/kg and still further increased to 10 or 15 mg/kg if initial control of symptoms is lost.[1] While this protocol undoubtedly may prove successful in many children, our patient shows that potentially serious side effects may occur even with a standard dose and that continued symptoms in a child with tetralogy treated with propranolol may be related to iatrogenic bradycardia rather than to continued episodes of severe cyanosis.

References

1 Garson A, Gillette PC, McNamara DG. Propranolol: the preferred palliation for tetralogy of Fallot. *Am J Cardiol* 1981;47:1099–104.

2 Pickoff AS, Zies L, Ferrer PL, *et al.* High dose propranolol therapy in the management of supraventricular tachycardia. *Pediatrics* 1979;94:144–6.

3 Anderson RH, Macartney FJ, Shinebourne EA, Tynan M, eds. *Paediatric cardiology.* London: Churchill Livingstone, 1987:777.

4 Eriksson BO, Thorén C, Zetterqvist P. Long-term treatment with propranolol in selected cases of Fallot's tetralogy. *Br Heart J* 1969;31:37–44.

5 Ponce FE, Williams LC, Webb HM, Riopel DA, Hohn AR. Propranolol palliation of tetralogy of Fallot: experience with long term drug treatment in pediatric patients. *Pediatrics* 1973;52:100–8.

6 Gillette PC, Garson A, Eterovic E, Neches W, Mullins CE, McNamara DG. Oral propranolol treatment in infants and children. *J Pediatr* 1978;92:141–4.

11.12.90

May 1989 Vol 61 No 5

British Heart Journal

A monthly journal of cardiology published in association with the British Cardiac Society

Editorial: Successful and unsuccessful coronary thrombolysis *M J Davies* **381**

Cineangiographic and pathological features of the infarct related vessel in successful and unsuccessful thrombolysis *T Onodera, H Fujiwara, M Tanaka, D-J Wu, M Matsuda, G Takemura, M Ishida, A Kawamura, C Kawai* **385**

Pathological changes after intravenous streptokinase treatment in eight patients with acute myocardial infarction *S G Richardson, D C Allen, P Morton, J G Murtagh, M E Scott, D B O'Keeffe* **390**

Favourable long term prognosis in patients with non-Q wave acute myocardial infarction not associated with specific electrocardiographic changes *W E Boden, R E Kleiger, R S Gibson, B R Reddy, K B Schechtman, D J Schwartz, R J Capone, R Roberts, and the Diltiazem Reinfarction Study Research Group* **396**

Risk factors for stroke and myocardial infarction in women in the United Kingdom as assessed in general practice: a case-control study *S G Thompson, G Greenberg, T W Meade* **403**

Prognostic significance of programmed ventricular stimulation in survivors of acute myocardial infarction *A K Bhandari, R Hong, A Kotlewski, N McIntosh, P Au, A Sankoorikal, S H Rahimtoola* **410**

Percutaneous transluminal angioplasty of left internal mammary artery grafts: two years' experience with a femoral approach *M R Bell, D R Holmes Jr, R E Vlietstra, D R Bresnahan* **417**

A new exercise test for the assessment of heart failure: use of a self powered treadmill *J Parameshwar, J-H E Dambrink, J Sparrow, C Wright, A Park, J Tweed, P A Poole-Wilson* **421**

Effect of temperature on rate of left ventricular pressure fall in humans *R A Luke, C E Gillbe, R S Bonser, M Paneth, D Somerset, J Thomas, D G Gibson* **426**

Balloon dilatation of stenosed Blalock-Taussig shunts *S A Qureshi, R P Martin, D F Dickinson, S Hunter* **432**

Proceedings of the British Cardiac Society **435**

Correspondence **483**

Notices **484**

Correction: Cardiac surgery for patients aged 65 years and older: a long term survival analysis *S Livesey, N Caine, D J Spiegelhalter, T A H English, J Wallwork* **484**

British Medical Association

ASTM CODEN: BHJUAV 61(5) 381–484 (1989)
ISSN 0007-0769

British Heart Journal

EDITOR Dennis Krikler ASSISTANT EDITORS M J Davies, Kim Fox, Peter Mills

EDITORIAL COMMITTEE
Clive P Aber Kate Bull Keith Dawkins Alan B Houston Barry R Keeton Michael Marmot
Alexander L Muir Paul J Oldershaw Philip A Poole-Wilson David B Shaw
Tom Treasure David E Ward John Watkins Peter Wilde
Editor: *British Medical Journal* Editor: *Cardiovascular Research*

TECHNICAL EDITOR Jane Dawson EDITORIAL ASSISTANT Anne Oliver
STATISTICAL ADVISER Stephen J W Evans

Notice to contributors

Papers relating to the heart and circulation should be sent in triplicate to the Editor, British Heart Journal, BMA House, Tavistock Square, London WC1H 9JR, and be prepared according to the *Uniform requirements for manuscripts submitted to biomedical journals* (Vancouver agreement) (*Br Med J* 1988;**296**:401–5). Authors are asked to complete a copy of the checklist provided (1988;**59**:47 (January issue)) when submitting their manuscripts for publication. The reference number given on the acknowledgement postcard sent out by the editorial office should be quoted on all subsequent correspondence and telephone inquiries. A covering letter must be signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. All authors will be required to transfer copyright of their articles to the journal before publication. (All material for possible publication (including Letters to the Editor) *must* be typed in *double spacing* with 4 cm margins.)

Ethical standards

Authors are expected to comply with the code of ethics known as the Declaration of Helsinki. Where appropriate, manuscripts should include a statement that the research protocol has been approved by the locally appointed ethics committee and that the informed consent of the subjects has been obtained.

Case reports should convey only the essential facts of a case and the discussion and bibliography be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and include no more than two Figures.

Abbreviations should *not* be used in the text, except for mathematical calculations and units of measurement.

References must be cited precisely according to the Vancouver agreement and be typed in *double spacing*. As a general rule, no more than three references should be cited for any one statement.

Authors are responsible for the accuracy of any references cited: these should be checked at source or with the listing in Index Medicus.

Units of measurement

All haematological and clinical chemistry measurements should be given as SI units. Blood pressures should be given in mm Hg. Measurements of length, height, weight, and volume should be reported in metric units and temperatures should be reported in degrees Celsius.

Tables must be typed on separate sheets and not in the text. Titles should be provided, and all abbreviations used must be given in full in a footnote.

Illustrations (for general requirements, please refer to *Br Heart J* 1984; **51:** 1–6).

Electrocardiograms: Black and white prints only should be sent and not the original tracings. If several tracings are grouped in a single Figure only a few complexes should be shown; the width should not exceed 14 cm unless a reduction in scale is possible.

Echocardiograms: Since these will be reproduced at a width of 7 cm or less all unnecessary or irrelevant detail (such as electronic writing) should be removed. Labelling must be superimposed directly on to the print itself and only where essential be shown on an accessory drawing. Echocardiograms obtained with 30° sector scans or bistable equipment or recorded on ultraviolet paper are not suitable for publication.

Figure legends must include an explanation of all abbreviations used in the Figure.

Copyright permission to reproduce material published elsewhere must be obtained in writing and acknowledged in the manuscript.

Proofs of articles accepted for publication will be sent for the author's approval. Proof corrections should be kept to a minimum.

Notice to subscribers

British Heart Journal is published monthly. The annual subscription rates are £97.00 inland and £113.00 overseas (USA $182·00). Combined rate: *British Heart Journal* and *Cardiovascular Research* £184 inland and £214 overseas (USA $350·00). Orders should be sent to The Subscription Manager, *British Heart Journal*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card. (For the convenience of readers in the USA subscription orders ($182) with or without payment may also be sent to British Medical Journal, Box 560B, Kennebunkport, Maine 04046. All inquiries, however, must be addressed to the Publisher in London.) **All copies are despatched by air-speed.** First class rates available on request.

COPYRIGHT © 1989 by the *British Heart Journal*. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission of the *British Heart Journal*.

Second class postage paid, Rahway NJ Postmaster: send address changes to: British Heart Journal c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

Br Heart J 1989;61:381–4

Editorial

Successful and unsuccessful coronary thrombolysis

M J DAVIES

From the British Heart Foundation Cardiovascular Unit, Department of Histopathology, St George's Hospital Medical School, London

Coronary thrombosis is a consequence of the exposure of subendothelial connective tissue, including types I and III collagen, to platelets passing over an atheromatous plaque.[1] This exposure may be the result of either superficial or deep intimal injury to the plaque; the two injury processes differ in some important aspects.[2]

Deep injury is the result of tears or fissures that extend from the arterial lumen into the depths of the intima and lead initially to the formation of thrombus within the plaque, which rapidly alters in shape and increases in size. A plaque undetected as causing a significant stenosis at angiography may subsequently undergo fissuring.[3 4] Intraluminal thrombus subsequently forms over the tear and is at first dominated by platelets. The final occluding thrombus is, however, rich in fibrin and red cells with few platelets.[3 4]

In superficial intimal injury the endothelium alone is lost; there is no deep intimal tear and thus no intraplaque thrombosis. Factors predisposing to a loss of the endothelial coat include a high grade stenosis and infiltration of the intima by monocytic cells containing lipid. Necropsy studies show that deep injury of the intima is three times more likely to be associated with occlusive thrombi than superficial injury.[5 6]

Fibrinolytic treatment often, but by no means always, restores anterograde flow in an occluded coronary artery.[3 7 8] This is not surprising to the pathologist because the final stage of an occluding thrombus, and in particular any distal propagation of the thrombus, is almost entirely composed of a loose network of fibrin packed with red cells, which would be expected to be susceptible to lysis. Thrombolytic treatment can, however, only reverse the thrombotic sequence of events to leave the residual plaque, which may have grown rapidly having an exposed intimal tear or merely have been denuded of endothelium. Clinical experience has led to the increased recognition of the short term factors that predispose to further occlusion from recurring intraluminal thrombus.[9]

The effect of thrombolysis on the coronary lesion

The process of recanalisation after fibrinolysis in the artery subtending a regional myocardial infarct has been followed by high resolution angiography.[3] As soon as some anterograde flow was restored, a lobulated mass of thrombus was seen in the lumen and adhering to a high grade stenosis which was often irregular in outline. Initially flow was re-established in the space between the vessel wall and the thrombus, which steadily became smaller; but a portion of mural thrombus commonly resisted lysis for some time.[10] In some reopened arteries (<20%) the appearance of a small crater (aneurysm) suggested that the intraplaque thrombus had also been lysed.[3] Complex irregular stenoses with residual intraluminal filling defects may persist up to a month after recanalisation.[11] Some arterial occlusions that were also presumed to be caused by thrombosis could not be reopened by thrombolytic treatment.

The rapid increase in the numbers of reports on the clinical aspects of fibrinolysis for acute coronary occlusion has not been matched by necropsy reports of either successful or unsuccessful fibrinolytic treatment and several important questions, which could have been answered by such studies, remain unanswered. Two papers in this issue of the *British Heart Journal* partly redress this imbalance.

Requests for reprints to Professor M J Davies, Department of Histopathology, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE

Onodera and his colleagues studied the pathological findings in 21 arteries in which occlusion had been treated by selective intracoronary fibrinolysis with urokinase.[12] This was successful in 15 and unsuccessful in six vessels; all the patients died within a week from cardiogenic shock or cardiac rupture. In 14 of the fifteen successfully reopened arteries all the intraluminal thrombus was removed, and there was a plaque fissure with residual intraplaque thrombus in 13. In the six arteries that were not reopened, residual thrombus remained within the lumen in five and there was also plaque fissuring. This study therefore confirmed the dominant role of plaque fissuring in invoking thrombosis, but found no clear morphological reason for the failures to reopen—except that in all six there was a proximal patent branch vessel that might have diverted flow of the fibrinolytic agent from the thrombus. None of the three occluded circumflex arteries was reopened.

The study by Richardson and his colleagues of five arteries that were successfully reopened by intravenous streptokinase also found that intraluminal thrombi were absent but found an underlying residual plaque fissure in only one artery.[13] In three arteries that remained occluded after thrombolysis, intraluminal thrombus was still present and there was an underlying deep intimal injury caused by a plaque fissure. If the pathological techniques were sound, and the methods described in the paper suggest that they were, these findings imply that thrombosis caused by superficial intimal injury is more easily treated by fibrinolytic treatment than that resulting from deep intimal injury.

There are good theoretical reasons why thrombi caused by major plaque fissures might be difficult to treat and might need more specific fibrinolytic agents, higher doses for longer periods, or intracoronary injection. Some fissures are so large that a flap of intima is raised, with extrusion of a plug of cholesterol and fragments of collagen which occlude the lumen. In other instances the intraintimal component of thrombus is so large that occlusion is the result of the mass of thrombus expanding the plaque itself. The fibrinolytic agent may not reach the interior of the plaque in all such cases; but the subsequent appearance of a small crater with overhanging edges in the angiogram suggests that it has in some reopened arteries.[5] Finally, a component of the intraluminal thrombus may be inherently more resistant to lysis; sequential angiograms suggest that this may be the area over the fissure itself.[5] Such sealing of the fissure orifice may be of benefit because it prevents more blood entering and expanding the plaque.

The overall message of the two papers is that the bigger the event in the intima that caused thrombosis the more difficult it may be to reopen the vessel by thrombolysis.

In an earlier necropsy study of arteries after recanalisation there was little evidence that fibrinolytic treatment had led to continuing growth of the plaque because of bleeding from the lumen into the intima, except when angioplasty and fibrinolysis were performed together.[14] Severe haemorrhage was seen around the angioplasty site in four patients who had been treated with fibrinolysis; in one the haematoma compressed the lumen externally. In contrast, five patients treated by angioplasty alone did not have such haemorrhage and in nine patients treated by streptokinase alone there was no recent intraplaque haemorrhage. The risk of combining angioplasty with fibrinolytic treatment derives from the intimal splits that are an integral part of successful procedures to relieve stenosis and that can extend into the medial/intimal junction in a plane in which there is a natural cleavage, allowing a haematoma to form. This plane is not entered by the intimal tears of natural plaque fissures.

The effect of thrombolysis on the myocardium

Restoration of flow to an infarcted area of myocardium leads to a striking and characteristic naked eye appearance at necropsy of haemorrhagic infarction (fig). A review of 93 necropsies of deaths after fibrinolytic treatment showed that 43% of the infarcts were red, whereas 95% of cases without reperfusion had a pale anaemic infarction.[14] The myocardium was red because of extensive haemorrhage into the interstitial tissues between the myocytes.[15] Interstitial haemorrhage is usually attributed to reperfusion of a capillary bed in which the endothelium has been damaged by hypoxia. Haemorrhagic infarction was reported to be less common after reperfusion by angioplasty without thrombolysis[14] suggesting that the thrombus or the lytic agent might release substances that damage the capillary endothelium.

A red infarction is of special consequence only if the haemorrhage extends outside the area of myocyte necrosis or alters the progress of repair by fibrosis. In animal models in which reversible ligation of the coronary artery was used to re-establish flow to an area of infarction, haemorrhage did not extend outside the area of myocardium at risk even when fibrinolytic treatment was given.[16] Nor did careful necropsy studies in man suggest that haemorrhage extended outside the areas in which there was evidence of ischaemic damage to myocytes.[13 15]

Some claim that intramyocardial haemorrhage can become so extensive that it prevents the expected

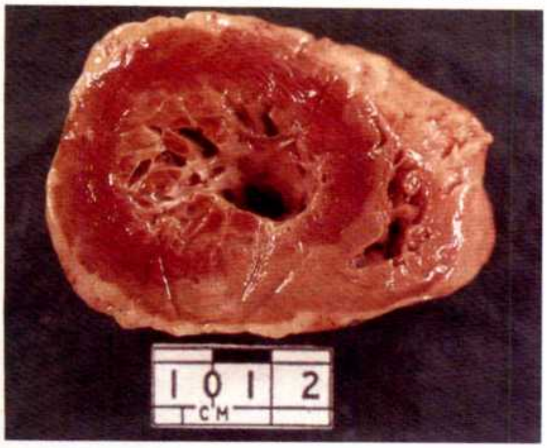


Figure *Haemorrhagic infarction seen at necropsy in a reperfused area of ischaemic necrosis.*

improvement in ventricular function after successful reperfusion,[14] but there is no firm proof of this. There are reports in some patients of pooling of angiographic media within the myocardium after fibrinolytic treatment.[17,18] These patients probably developed an intramyocardial haematoma; which raises the question whether the risk of myocardial rupture is higher after fibrinolysis. A further possible factor predisposing to rupture is a suggested delay in repair by fibrosis in haemorrhagic infarcts.[19] The evidence for this in man is based largely on a comparison of the histological appearances of an anaemic infarct and a haemorrhagic infarct in the same patient. The clinical evidence that both infarcts were the same age was not strong, and the hypothesis was not confirmed in experimental models of haemorrhagic infarction.[20]

Five (24%) of the series of 21 patients reported by Onodera *et al* who died soon after fibrinolytic had external cardiac rupture,[12] whereas cardiac rupture was reported in 10 and 20% in two necropsy studies of in hospital infarction without fibrinolytic treatment.[21,22] External rupture of an infarct may occur early (within 24 hours) if there is shearing at the border between viable and non-viable myocardium, or later if an established infarct expands and softens.[23] Two large multicentre studies suggested a slight preponderance of early deaths (0–1 day) in those treated with streptokinase, and analysis of the data indicated that the preponderance was the result of cardiac rupture, which was reduced in frequency by intravenous atenolol.[24,25] If the myocardium ruptures some time after the onset of infarction, an endocardial tear and intramyocardial haematoma often precede the formation of either a haemopericardium or ventricular aneurysm. This process could be exacerbated by fibrinolytic treatment. Large trials of fibrinolytic treatment in which the cause of death is accurately established by necropsy will be needed to establish whether this is so. In the ISAM trial there were 10 cases of cardiac rupture in the treated group and 13 in the placebo group[26]; in the ISIS-2 trial there were more cardiac ruptures in the placebo group than in those treated with streptokinase (76/74), aspirin (81/69), or both (38/31).[27] A review of the reported data from eight trials up to 1979 showed equal numbers of cardiac ruptures in the treated and placebo groups.[28] If fibrinolytic treatment has any effect on late cardiac rupture it is likely to reduce the rate slightly because it limits infarct size.

References

1 Fuster V, Badimon L, Cohen M, Ambrose JA, Badimon JJ, Chesbro J. Insight into the pathogenesis of acute ischemic syndromes. *Circulation* 1988;77:1213–20.

2 Davies MJ. Thrombosis and coronary atherosclerosis. In: Julian DG, Kubler W, Norris RM, Swan HJC, Collen D, Verstraete M, eds. *Thrombolysis in cardiovascular disease.* New York: Marcel Dekker, 1989:25–44.

3 Brown BG, Gallery CA, Badger RS, *et al.* Incomplete lysis of thrombus in the moderate underlying atherosclerotic lesion during intracoronary infusion of streptokinase for acute myocardial infarction: quantitative angiographic observations. *Circulation* 1986; **73**:653–61.

4 Little WC, Constantinescu M, Applegate RJ, *et al.* Can coronary angiography predict the sight of a subsequent myocardial infarction in patients with mild to moderate coronary artery disease? *Circulation* 1988; **78**:1157–66.

5 Davies MJ, Thomas AC. The pathological basis and microanatomy of occlusive thrombus formation in human coronary arteries. *Philos Trans R Soc Lond [Biol]* 1981;**294**:225–9.

6 Falk E. Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis. Characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi. *Br Heart J* 1983;**50**:127–34.

7 Schroder R, Biamiono G, Leitner E-R. Intravenous short-term infusion of streptokinase in acute myocardial infarction. *Circulation* 1983;**67**:536–48.

8 Koren G, Weiss AT, Hasin Y, *et al.* Prevention of myocardial damage in acute myocardial ischaemia by early treatment with intravenous streptokinase. *N Engl J Med* 1985;**313**:384–9.

9 Harrison DG, Ferguson DW, Collins SM, *et al.* Rethrombosis after reperfusion with streptokinase: importance of geometry of residual lesions. *Circulation* 1984;**69**:991–9.

10 Isner JM, Konstam MA, Fortin RV, Lefebvre M, Salem DN. Delayed thrombolysis of streptokinase-resistant occlusive thrombus: documentation by pre- and postmortem coronary angiography. *Am J Cardiol* 1983;**52**:210–1.

11 Nakagawa S, Hanada Y, Koiwaya Y, Tanaka K. Angiographic features in the infarct related artery after intracoronary urokinase followed by prolonged anticoagulation. Role of ruptured atheromatous plaque and adherent thrombus in acute myocardial infarction in vivo. *Circulation* 1988;78:1335–44.

12 Onodera T, Fujiwara H, Tanaka M, *et al.* Cineangiographic and pathological features of the infarct-related vessel in successful and unsuccessful thrombolysis. *Br Heart J* 1989;61:385–9.

13 Richardson SG, Allen DC, Morton P, Murtagh JG, Scott ME, O'Keeffe DB. Pathological changes after intravenous streptokinase treatment in eight patients with acute myocardial infarction. *Br Heart J* 1989;61:390–5.

14 Waller BF, Rothbaum DA, Pinkerton CA, *et al.* Status of the myocardium and infarct-related coronary artery in 19 necropsy patients with acute recanalization using pharmacologic (streptokinase, r-tissue plasminogen activator), mechanical (percutaneous transluminal coronary angioplasty) or combined types of reperfusion therapy. *J Am Coll Cardiol* 1987; 9:785–801.

15 Fujiwara H, Onodera T, Tanaka M. A clinicopathological study of patients with haemorrhagic myocardial infarction treated with selective coronary thrombolysis with urokinase. *Circulation* 1986;73:749–57.

16 Kloner RA, Alker KJ. The effect of streptokinase on intramyocardial hemorrhage, infarct size, and the no-reflow phenomenon during coronary reperfusion. *Circulation* 1984;70:513–21.

17 Yasuno M, Endo S, Takakashi M, *et al.* Angiographic and pathologic evidence of hemorrhage into the myocardium after coronary reperfusion. *Angiology* 1984;35:797–801.

18 Little WC, Rogers EW. Angiographic evidence of hemorrhagic myocardial infarction after intracoronary thrombolysis with streptokinase. *Am J Cardiol* 1983;51:906–8.

19 Mathey DG, Schofer J, Kuck K-H, Beil U, Klöppel G. Transmural haemorrhagic myocardial infarction after intracoronary streptokinase. Clinical, angiographic, and necropsy findings. *Br Heart J* 1982;48:546–51.

20 Althaus U, Gwirner HP, Bauer H, Hamburger S, Roos B. Consequences of myocardial reperfusion following temporary coronary occlusion in pigs: effects on morphologic, biochemical and hemodynamic findings. *Eur J Clin Invest* 1977;7:437–43.

21 Davies MJ, Woolf N, Robertson WB. Pathology of acute myocardial infarction with particular reference to occlusive coronary thrombi. *Br Heart J* 1976;38: 659–64.

22 Dellborg M, Held P, Swedberg K, Vedin A. Rupture of the myocardium: occurrence and risk factors. *Br Heart J* 1985;54:11–6.

23 Becker AE, Vanmantgem JP. Cardiac tamponade—a study of 50 hearts. *Eur J Cardiol* 1975;3:349–58.

24 The ISIS-1 (First International Study of Infarct Survival) Collaborative Group. Mechanisms for the early mortality reduction produced by beta blockade started early in acute myocardial infarction. ISIS 1. *Lancet* 1988;i:921–3.

25 The GISSI Study Group. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;i:397–401.

26 The ISAM Study Group. A prospective trial of intravenous streptokinase in acute myocardial infarction (I.S.A.M): mortality, morbidity and infarct size at 21 days. *N Engl J Med* 1986;314:1465–71.

27 The ISIS Study Group. Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17 187 cases of suspected acute myocardial infarction. ISIS-2. *Lancet* 1988;ii:349–60.

28 Yusuf S, Collins R, Peto R, *et al.* Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction. Overview of results on mortality, reinfarction and side-effects from 33 randomized controlled trials. *Eur Heart J* 1985;6:556–85.

Br Heart J 1989;61:385–9

Cineangiographic and pathological features of the infarct related vessel in successful and unsuccessful thrombolysis

TOMOYA ONODERA, HISAYOSHI FUJIWARA, MASARU TANAKA, DER-JINN WU, MITSUO MATSUDA, GENZOU TAKEMURA, MORIHARU ISHIDA, ATSUSHI KAWAMURA, CHUICHI KAWAI

From the Third Division, Department of Internal Medicine, Kyoto University, Kyoto, Japan

SUMMARY The postmortem histology and the results of cineangiography after selective intracoronary thrombolysis in vessels that were recanalised and in those that were not were compared in 21 patients who died within seven days (mean 2 days) of selective intracoronary thrombolysis. There was a persistent intraluminal thrombus in the infarct related coronary artery in five of six segments in which recanalisation was unsuccessful and in one of 15 segments in which recanalisation was successful. Rupture and haemorrhage of the atheromatous plaque were seen in most of the infarct related segments, both in those in which recanalisation was achieved and in those in which it was not. Irregular narrowing and filling defects on the coronary cineangiograms were associated with rupture and haemorrhage of the atheromatous plaque.

These results suggest that failure of coronary thrombolysis to recanalise the infarct related artery does not indicate that the occlusion was not caused by thrombus.

Selective intracoronary thrombolysis and percutaneous transluminal coronary angioplasty are increasingly being performed in patients with acute myocardial infarction.[1–7] Such treatment often results in recanalisation[1–3] and reduces mortality.[4] It may, however, cause haemorrhagic infarction.[8]

It has been reported that the angiographic morphology of a stenosis reflects the histological findings, such as intraluminal thrombus or rupture of an atheromatous plaque.[9–12] As far as we know, no one has attempted to correlate the angiographic picture and the histological examination in patients treated with selective intracoronary thrombolysis. Also, there are only two reports on the histopathogenesis of successful and unsuccessful recanalisation; both were small studies.[13 14]

We have examined the correlation between the angiographic appearance of lesions and the underlying histopathology after selective intracoronary thrombolysis.

Requests for reprints to Dr Chuichi Kawai, Third Division, Department of Internal Medicine, Faculty of Medicine, Kyoto University, Sakyo-ku, Kyoto 606, Japan

Accepted for publication 29 November 1989

Patients and methods

We studied 21 patients (14 men and seven women, aged 45–83) who died an hour to seven days (2 (2) days) after selective intracoronary thrombolysis (table 1). Sixteen patients died of cardiogenic shock and five of cardiac rupture. Every patient had selective intracoronary thrombolysis an hour to nine hours after the onset of acute myocardial infarction.

In all of them acute myocardial infarction had been diagnosed on the basis of severe chest pain, serial electrocardiographic changes in the ST-T segment or the appearance of abnormal Q waves or both, and an increase in serum concentrations of creatine kinase. After the vessel that had caused the acute infarction was identified by selective coronary cineangiography, 0·5 mg of glyceryl trinitrate was slowly injected into it. If no change was noted in the angiographic appearance of the vessel, urokinase was continuously and selectively infused at a rate of 24 000 units/min. If the occluded artery was not recanalised after the administration of a large amount of urokinase (720 000–1 680 000 units) the attempt was stopped. After selective intracoronary thrombolysis, the patients were treated with aspirin

Table 1 *Summary of patients according to interval from selective intracoronary thrombolysis (SICT) to death*

Case no	*Age*	*Sex*	*Time from onset of AMI to to SICT*	*UK (× 10) IU*	*Time from SICT to death*	*Cause of death*
1	60	M	6 h	60	1 h	Rupture
2	77	M	3 h	36	1 h	Shock
3	70	F	1 h	96	2 h	Shock
4	68	F	5 h	24	3 h	Shock
5	72	M	2 h	48	3 h	Shock
6	56	M	9 h	72	3 h	Shock
7	53	F	3 h	72	7 h	Shock
8	53	M	6 h	96	9 h	Shock
9	83	M	2 h	24	12 h	Shock
10	70	F	4 h	60	16 h	Shock
11	45	M	2 h	60	19 h	Shock
12	53	M	6 h	24	25 h	Shock
13	62	F	5 h	108	2 days	Rupture
14	72	M	3 h	36	2 days	Rupture
15	71	M	8 h	96	3 days	Rupture
16	74	M	3 h	24	3 days	Shock
17	51	M	2 h	96	4 days	Shock
18	63	F	3 h	0	4 days	Rupture
19	70	M	5 h	74	5 days	Shock
20	75	M	4 h	168	6 days	Shock
21	75	F	9 h	0	7 days	Shock
Mean (1SD)	65 (10)		4 (2) h	59 (41)	1·8 (2·3) days	

AMI, acute myocardial infarction, UK, urokinase; Rupture, cardiac rupture, Shock, cardiogenic shock.

(300 mg/day) and a low dose of heparin (5000 units every 8–12 hours).

All the angiograms were reviewed by three experienced cardiologists, according to the system recommended by the American Heart Association.[15] To evaluate the stenosis the arteriogram was magnified (× 5) and the luminal diameter was measured with callipers. On the basis of the angiographic appearance we classified all the segments with stenosis of 75%–99% by diameter as stenoses with smooth narrowing, irregular borders, or filling defects.

The hearts were fixed in 10% formalin. The epicardial coronary arteries were decalcified (if necessary) and cut transversely and serially from the ostium to the periphery every 2–3 mm and examined directly. The coronary arteries were divided into 15 segments according to the reporting system recommended by the American Heart Association.[15] The point with the most severe stenosis in each of the 15 segments of the coronary arteries was embedded in paraffin. Then we used a microtome to obtain sections of 4 μm. We used branches of the coronary arteries as landmarks to ensure that specific angiographic lesions were examined histologically. The stenosis was examined again after the preparation was stained with elastic van Gieson. In the segments with stenosis of ⩾75% the sections with the most severe stenosis and the segments 3 mm on either side of them were sectioned serially every 100 μm. All sections were stained with haematoxylin eosin and elastic van Gieson. They were examined for intraluminal thrombus, haemorrhage in the atheromatous plaque, or rupture of the atheromatous plaque.

So that we could compare the results of cineangiography and histology we ensured that the same branches of the major coronary arteries were examined both by coronary angiography and histological examination.

STATISTICAL ANALYSIS

Data were analysed by χ^2 test with Yates' correction and by one way analysis of variance to test for multiple comparisons. A difference of $p < 0{\cdot}05$ was regarded as significant.

Results

We classified the 21 infarct related segments as six with complete occlusion despite coronary thrombolysis and 15 without complete occlusion (table 2). Five of the six occluded segments contained intraluminal thrombus but only one of the segments without occlusion did ($p < 0{\cdot}05$) (figure). Rupture of the atheromatous plaque and haemorrhage in the atheromatous plaque were equally common in both groups.

Thirty eight segments from the study group of 21 patients showed high grade (> 75%) stenosis. This total included 15 stenoses that were displayed by angiography after thrombolysis. Fifteen of the stenoses showed angiographically irregular narrowing, two intraluminal filling defects, and 21 smooth narrowing (table 3, figure). Thrombus, rupture of the atheromatous plaque, and haemorrhage in the atheromatous plaque and infarct related arteries were seen in 0, 80, 80, and 67% in the segments with angiographically irregular narrowing and in 0, 10, 5, and 14% in the segments with angiographically smooth narrowing ($p < 0{\cdot}05$). The two segments with angiographically detected filling defects were infarct related arteries with rupture and haemorrhage in the atheromatous plaque; thrombus was seen in one.

Table 2 *Histological findings and stenosis shown by coronary cineangiography (CAG) in the infarct related segments*

CAG results	*No of patients*	*Thrombus*	*Rupture of atheroma*	*Haemorrhage in atheroma*
Persistent occlusion	6	5 (84%)*	5 (84%)	5 (84%)
Patent (but < 75% stenosis)	15	1 (7%)*	13 (87%)	12 (80%)

*$p < 0{\cdot}05$.

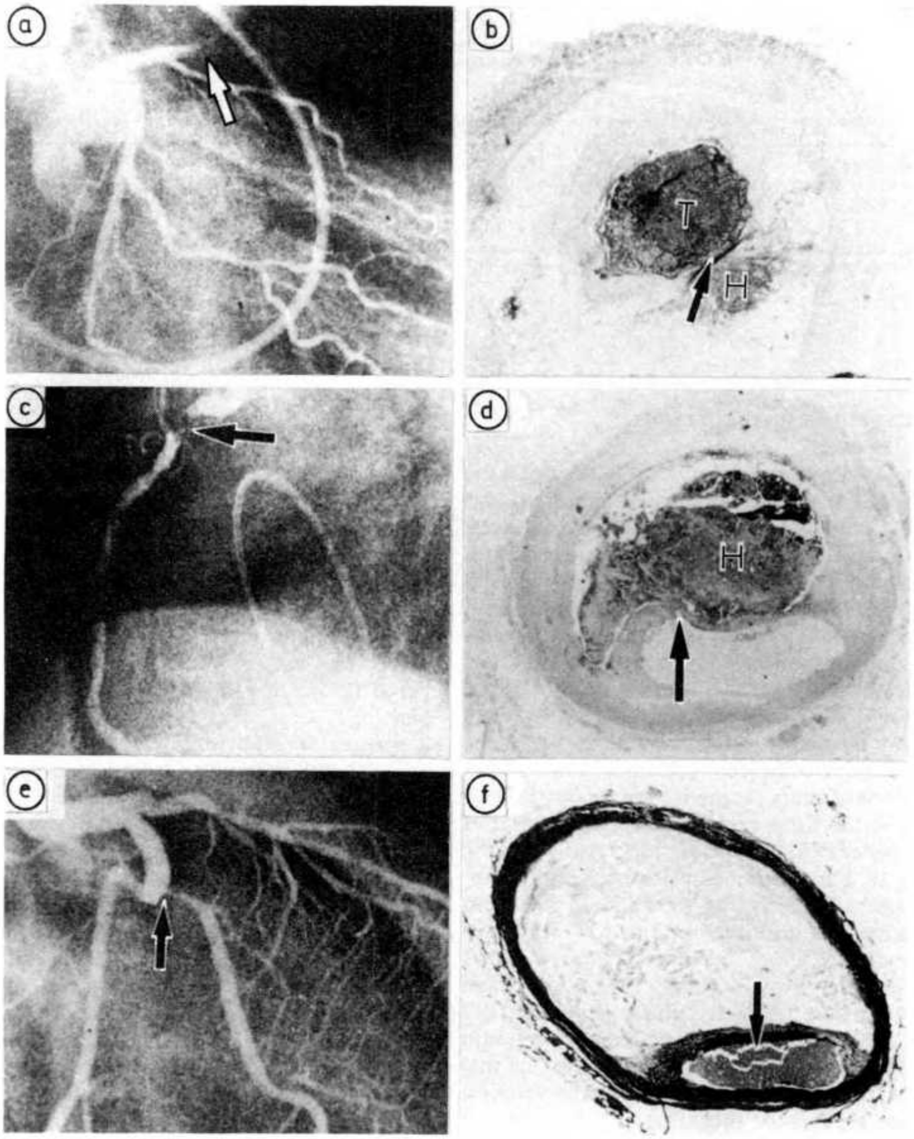


Figure *Histology of the coronary artery and angiographic findings. (a) left coronary angiogram of patient 13. (b) Histological section of segment 6 of the patient. Segment 6 showed complete occlusion (arrow) in coronary cineangiography despite intracoronary thrombolysis. Histology showed an intraluminal thrombus (T) and haemorrhage (H) and rupture (arrow) of the atheromatous plaque. (c) Right coronary angiogram of patient 9. (d) Histological section of segment 1 of patient 9. In coronary cineangiography, segment 1 showed recanalisation with irregular narrowing after thrombolysis. Segment 1 showed haemorrhage (H) and rupture (arrow) of the atheromatous plaque and no thrombus. (e) Left coronary angiogram of patient 18. (f) Histological section of segment 11 of patient 18. Coronary cineangiography showed smooth narrowing with 90% stenosis (arrow). Histological examination found neither intraluminal thrombus nor rupture or haemorrhage of the atheromatous plaque in the segment. The arrow indicates the lumen.*

Table 3 *Relation between the morphological findings at coronary cineangiography and histological findings*

		Histological findings			
Angiographic morphology	*No of segments*	*Thrombus*	*Rupture of atheroma*	*Haemorrhage in atheroma*	*Infarct related segments*
Irregular narrowing	15	0 (0%)	12 (80%)*	12 (80%)*	10 (67%)*
Intraluminal filling defect	2	1 (50%)	2 (100%)	2 (100%)	2 (100%)
Smooth narrowing	21	0 (0%)	2 (10%)*	1 (5%)*	3 (14%)*
Mean	38	1 (3%)	16 (42%)	15 (39%)	15 † (40%)†

*$p < 0.05$, irregular *v* smooth narrowing. †Infarct related segments in which occlusion was not complete

Discussion

PATHOGENESIS OF UNSUCCESSFUL RECANALISATION

We found (*a*) intraluminal thrombus in nearly all the infarct related arteries in which recanalisation was unsuccessful, but it was rare in recanalised segments; (*b*) rupture and haemorrhage of the atheromatous plaque in most of the infarct related coronary arteries irrespective of the success of recanalisation. Without coronary thrombolysis 90% of patients have thrombus in the infarct related coronary artery.[16 17] These data indicate that infarct related arteries that are successfully recanalised by thrombolysis were occluded by thrombus. None the less, in five of the six patients with complete occlusion of the infarct related coronary artery recanalisation was unsuccessful. None of the three occluded circumflex arteries were reopened. Merx *et al* reported that the frequency of recanalisation is low in the left circumflex artery.[18] In five of six patients in whom recanalisation was unsuccessful a nearby branch of the left coronary artery that was unrelated to the infarct was widely patent. It may be that urokinase flowed mainly into this non-occluded artery and did not reach the thrombus. The absence of thrombus in the arteries with successful recanalisation shows that the lysis of intraluminal thrombi is usually complete if urokinase reaches the thrombus. Thus the site of thrombus may be important to the success of recanalisation.

In the recanalised arteries of patients treated with selective intracoronary thrombolysis, the residual stenosis was caused by atheromas with rupture and haemorrhage. However, Mattfeldt *et al* reported that they did not see rupture and haemorrhage of the atheromatous plaque in three patients with successful recanalisation.[13] But rupture and haemorrhage of atheromatous plaques are found in about 90% of patients with acute myocardial infarction not treated with intracoronary thrombolysis[16 17 19 20] and recanalisation is successful in about 80% of patients treated with intracoronary thrombolysis.[18] So the results reported by Mattfeldt *et al* may merely reflect the small number (three) of patients in their study.

CINEANGIOGRAPHIC RESULTS

Our results showed that the irregular narrowing and filling defects on cineangiograms coincided with rupture and haemorrhage of atheromatous plaques, whereas a smooth narrowing showed that there was no rupture or haemorrhage. We also found that the infarct related arteries showed frequent irregular narrowing and filling defects. These findings confirmed the results of Levin and Fallon,[10] who compared the results of postmortem angiography and histology, and the cineangiography studies of Terrosu *et al*[9] and Ambrose *et al*.[11 12] These groups found that thrombi were as important as rupture and haemorrhage of atheromatous plaques in the pathogenesis of irregular narrowings. We were not able to establish the relation between thrombi found by histology and irregular narrowing or filling defects found by cineangiography because after coronary thrombolysis there were few thrombi present.

The results of our study suggest that failure of coronary thrombolysis to recanalise the infarct related artery does not indicate that the occlusion was not caused by a thrombus. We also found that findings at angiography accorded well with the histological features of coronary atherosclerosis.

We thank S Tomita and M Jinnai for their technical assistance and Ms M Ohara for reading the manuscript.

This study was supported in part by a research grant from the Ministry of Education, Science, and Culture, Japan.

References

1 Rentrop P, Blanke H, Karsch KR, Kreuzer H. Initial experience with transluminal recanalisation of the recently occluded infarct-related coronary artery in acute myocardial infarction—comparison with conventionally treated patients. *Clin Cardiol* 1979;2: 92–105.

2 Ganz W, Buchbinder N, Marcus H, *et al.* Intracoronary thrombolysis in evolving myocardial infarction. *Am Heart J* 1981;**101**:4–13.

3 Markis JE, Malagold M, Parker JA, *et al.* Myocardial salvage after intracoronary thrombolysis with streptokinase in acute myocardial infarction. *N Engl J Med* 1981;**305**:777–82.

4 Ferguson DW, White CW, Schwartz JL, *et al.* Influence of baseline ejection fraction and success of thrombolysis on mortality and ventricular function after acute myocardial infarction. *Am J Cardiol* 1984; **54**:705–11.

5 Hartzler GO, Rutherford BD, McConahay DR, *et al.* Percutaneous transluminal coronary angioplasty with and without thrombolytic therapy for treatment of acute myocardial infarction. *Am Heart J* 1983; **106**:965–73.

6 Dodge HT, Sheehan FN, Mathey DG, Brown BG, Kennedy JW. Usefulness of coronary artery bypass graft surgery or percutaneous transluminal angioplasty after thrombolytic therapy. *Circulation* 1985;**72**(suppl V):39–45.

7 Prida XE, Holland JP, Feldman RL, *et al.* Percutaneous transluminal coronary angioplasty in evolving acute myocardial infarction. *Am J Cardiol* 1986;**57**: 1069–74

8 Fujiwara H, Onodera T, Tanaka M, *et al.* A clinicopathologic study of patients with hemorrhagic infarction treated with selective coronary thrombolysis with urokinase. *Circulation* 1986;**73**:749–57.

9 Terrosu P, Vibba GV, Contini GM, Franceschino V. Angiographic features of the coronary arteries during intracoronary thrombolysis. *Br Heart J* 1984;**52**: 154–63.

10 Levin DC, Fallon JT. Significance of the angiographic morphology of localised coronary stenoses: histopathologic correlations. *Circulation* 1982;**66**:316–20.

11 Ambrose JA, Winters SL, Stern A, *et al.* Angiographic morphology and the pathogenesis of unstable angina pectoris. *J Am Coll Cardiol* 1985;**5**:609–16.

12 Ambrose JA, Winters SL, Arora RR, *et al.* Coronary angiographic morphology in myocardial infarction: a link between the pathogenesis of unstable angina and myocardial infarction. *J Am Coll Cardiol* 1985;**6**: 1233–8.

13 Mattfeldt T, Schwarz F, Schuler G, Hoffman M, Kubler W. Necropsy evaluation in seven patients with evolving acute myocardial infarction treated with thrombolytic therapy. *Am J Cardiol* 1984; **54**:530–4.

14 Mathey D, Schofer J, Kuck K-H, Beil U, Kloppel G. Transmural, hemorrhagic myocardial infarction after intracoronary streptokinase: clinical, angiographic, and necropsy findings. *Br Heart J* 1982;**48**:546–51

15 Austen WG, Edwards JE, Frye RL, *et al.* A reporting system on patients evaluated for coronary artery disease. *Circulation* 1975;**51**:7–40.

16 Ridolfi RL, Hutchins GM. The relationship between coronary artery lesions and myocardial infarcts: ulceration of atherosclerotic plaques precipitating coronary thrombosis. *Am Heart J* 1977;**93**:468–86.

17 Horie T, Sekiguchi M, Hirosawa K. Coronary thrombosis in pathogenesis of acute myocardial infarction: histopathological study of coronary arteries in 108 necropsied cases using serial section. *Br Heart J* 1978;**40**·153–61.

18 Merx W, Dorr R, Rentrop P, *et al.* Evaluation of the effectiveness of intracoronary streptokinase infusion in acute myocardial infarction: postprocedure management and hospital course in 204 patients. *Am Heart J* 1981;**102**:1181–7.

19 Chapman I. Morphogenesis of occluding artery thrombosis. *Arch Pathol* 1965;**80**·256–61.

20 Friedman M, Van Den Bovenkamp GJ. The pathogenesis of a coronary thrombus. *Am J Pathol* 1966;**48**: 19–31.

Br Heart J 1989;61:390–5

Pathological changes after intravenous streptokinase treatment in eight patients with acute myocardial infarction

S GEOFFREY RICHARDSON, DEREK C ALLEN, PATRICIA MORTON, J GERARD MURTAGH, MICHAEL E SCOTT, D BARRY O'KEEFFE

From the Cardiac Unit and Histopathology Department, Belfast City Hospital, Belfast

SUMMARY At necropsy five of eight patients (mean age 57 years) who died after intravenous streptokinase treatment for severe acute myocardial infarction (mean Peel index = 18) were found to have a patent infarct related coronary artery. Coronary artery stenoses were caused by fibrofatty atheromatous plaques; there were no residual thrombi in the lumen or acute intimal lesions. Three of these infarcts were of partial thickness (less than two thirds wall width) with sparing of the outer third of the myocardium and subendocardial zones. In the other three patients the infarct related coronary arteries remained histologically closed with residual lumen thrombi and underlying intimal lesions. Two infarcts were transmural. Six of the eight infarcts were noticeably haemorrhagic. Myocardial haemorrhage was confined to areas of necrotic myocardium and did not affect viable regions.

These findings suggest that thrombus overlying a complex lesion may be more difficult to lyse than thrombus overlying a simple fibrofatty plaque. They also suggest that myocardial haemorrhage outside the infarct area, which might lead to cardiac rupture or delayed healing, does not usually occur.

There has been relatively little reported work on human cardiac pathology after thrombolytic treatment and several points are not clear. Myocardial haemorrhage may occur after coronary reperfusion. Although the weight of evidence suggests that this only occurs in areas of irreversibly damaged myocardium, fatal haemorrhagic myocardial infarction has been described after intracoronary streptokinase treatment.[1 2] It has also been suggested that the success of coronary artery recanalisation depends, in part, on the morphologic features of the coronary occlusion and that reperfusion after successful thrombolysis may lead to a different pattern of muscle fibre necrosis in the irreversibly injured infarct areas.[3]

The aims of this study were to characterise the changes in the myocardium after streptokinase treatment and to determine whether streptokinase treatment directly contributed to mortality in any patient. The patency of the infarct related coronary artery was examined in relation to the morphology of the underlying coronary lesion and to the extent of myocardial damage.

Patients and methods

Over a 15 month period necropsies were performed on eight patients who died after receiving thrombolytic treatment for acute myocardial infarction. Patients less than 70 were treated with 1·5 million units of streptokinase intravenously if they had chest pain lasting < 6 h, typical ST segment elevation of at least 2 mm in the precordial chest leads or 1 mm in the standard limb leads, evidence of severe myocardial infarction (Peel coronary prognostic index > 13[4]), and no specific contraindications to thrombolytic treatment or anticoagulation. Thirteen patients died in hospital after thrombolytic treatment. Consent for a necropsy was not given in five cases.

PATHOLOGY

A full necropsy was carried out on each patient within 30 hours after death. The hearts were weighed and the external surfaces inspected. The ascending aortic

Requests for reprints to Dr S Geoffrey Richardson, Cardiac Unit, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB.

Accepted for publication 2 February 1989

trunk was cut close to the valve ring and the coronary artery ostia were identified and inspected. The ostium of the infarct related main arterial trunk was cannulated with a 9 French gauge coronary catheter that was tied in place by means of a periarterial suture. The artery was injected with a solution of radiocontrast material under fluoroscopic imaging. Arterial stenoses and occlusions were identified and radiographic films were taken in different planes. The non-infarct arterial trunk was injected, and the injection medium was flushed out of the coronary arteries with physiological saline. The hearts were then fixed in formalin for 48 hours.

We used angiograms obtained after death to guide dissection; the coronary arteries were cut into serial transverse blocks every 2 mm. Stenosed segments were removed and decalcified. Histological sections (5 μm) were cut and examined throughout each block. The hearts were opened and inspected. Multiple transverse horizontal slices of the left ventricle were produced, in which the infarct appearance was noted and linear measurements of infarct size were made. Histological sections were stained with haematoxylin and eosin and the Martius scarlet blue technique. The severity of coronary artery stenosis was assessed by measuring the residual cross sectional luminal area as a percentage of the assumed original cross sectional area of the vessel (the area encircled by the internal elastic lamina). We measured the vessel diameters with an eyepiece graticule.[5] The cross sectional area (A) was calculated from the maximum lumen diameter (D) and the minimum lumen diameter (d) by the formula: $A = \pi(D \times d)/4$ (this formula assumes an elliptical cross section).

Results

MORTALITY DATA

Six patients had an anterior wall infarction and one patient had an inferior wall infarction (table 1). In one patient there was evidence of combined anterior and inferior wall infarction. Myocardial infarction was assessed as severe in all patients at clinical presentation (mean Peel coronary prognostic index = 18, range 14–21). At admission all patients had systemic hypotension and five had left ventricular failure (patients 3, 5, 6, 7, and 8). The mean time from onset of ischaemic chest pain to treatment with streptokinase was 1·8 hours (range 30 minutes to three hours). After streptokinase treatment cardiac failure persisted in five patients (patients 3, 5, 6, 7, and 8). Three patients (patients 1, 2, and 4) initially made a good recovery. In patients 1 and 4 recurrent ischaemic chest pain and electrocardiographic ST elevation suggested coronary reocclusion. Clinical deterioration and death followed. Patient 2 developed abdominal pain and refractory hypotension on the third week after streptokinase treatment. Necropsy confirmed the presence of mesenteric embolism.

Percutaneous transluminal coronary angioplasty of a lesion of the proximal left coronary artery was successfully performed on patient 5 two days after streptokinase treatment. Despite this intervention cardiac failure and hypotension persisted. This patient's clinical course was also complicated by gastrointestinal haemorrhage.

PATHOLOGY

The infarct related coronary artery was patent in five patients (table 2). All had severe atheromatous stenoses. In four patients the stenosis was caused by an uncomplicated, obstructive fibrofatty arterial plaque with no residual thrombus in the lumen or acute intimal lesion (fig 1). The fifth showed an intimal and medial longitudinal split capped by thrombus. This patient had coronary angioplasty after streptokinase treatment.

The infarct related coronary artery remained occluded in three cases. There was a complicated atheromatous stenosis in all three. An acute intimal lesion was associated with occlusive thrombus in the lumen (fig 2).

Haemorrhagic myocardial infarction was present in four of five patients with an open infarct related coronary artery (table 3). In three of these five

Table 1 *Summary of clinical findings*

Case no	*Age and sex*		*Infarct site*	*Peel index*	*Time to treatment (h)*	*Clinical course*	*Time of death (day)*
1	50	M	A	14	1·5	Reocclusion day 5	5
2	67	M	A	21	1·7	Mesenteric embolism	21
3	67	M	A	17	3·0	Refractory cardiac failure	4
4	58	F	A/I	15	1·5	Reocclusion day 3	3
5	55	M	A	20	3·0	Progressive cardiac failure plus gastrointestinal bleeding	6
6	62	M	A	18	2·0	Refractory cardiac failure	6
7	40	M	A	18	2·5	Refractory cardiac failure	10
8	49	M	I	20	0·5	Refractory cardiac failure	8

A, anterior; I, inferior.

Table 2 *Pathological characteristics of the infarct related coronary artery*

		Infarct artery				
Case no	*Infarct site*	*Patency**	*Site*	*Stenosis (%)*	*Plaque*	*Thrombus*
1	A	+	LAD	91	Fibrous	−
2	A	+	LMS	80	Fibrous	−
3	A	+	LAD	80	Fibrous	−
4	A/I	+	LAD/RCA	78	Fibrous	−
5	A	+	LAD	78	Rupture	+
6	A	−	LAD	98	Rupture	+
7	A	−	LAD	90	Rupture	+
8	I	−	RCA	97	Rupture	+

*Infarct artery: +, open; −, closed.
LMS, left main stem; LAD, left anterior descending artery; RCA, right coronary artery.

patients myocardial infarction was of partial wall thickness (fig 3). One case showed a transmural myocardial infarction and one a mixed picture with areas of both partial thickness and transmural myocardial infarction.

Two of the three patients with an occluded infarct related artery were associated with transmural myocardial infarction and one with a partial thickness infarct (table 3).

Histological examination confirmed the haemorrhagic nature of the infarcts. There were abundant aggregates of red blood cells in the interstitium between necrotic myofibres. This interstitial haemorrhage was associated with necrosis of the microvasculature. Haemorrhage was not present in viable muscle. Partial thickness myocardial infarcts were characterised by preservation of a narrow subendocardial zone and the outer one third of the myocardium. In two patients, vessels containing small embolic thrombi were seen in the myocardium.

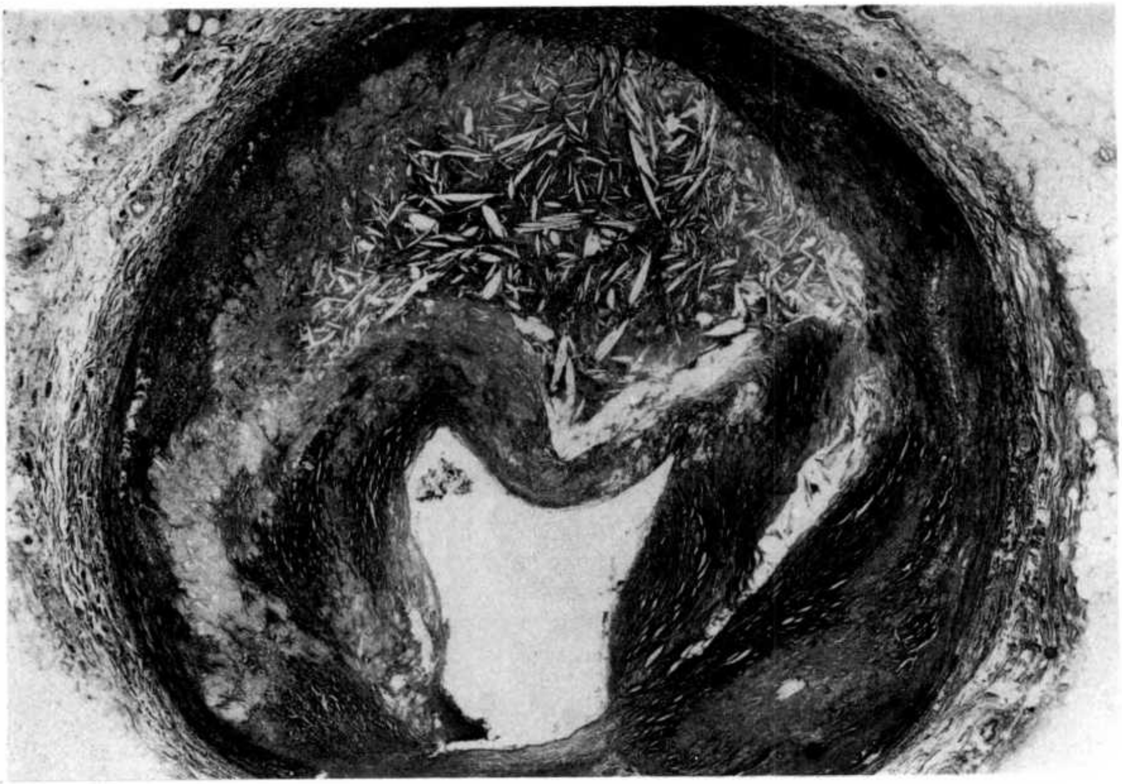


Fig 1 *The left anterior descending artery in patient 1 was stenosed by a fibrofatty atheromatous plaque. The lumen was patent and the intima intact. Martius scarlet blue (original magnification, × 40).*

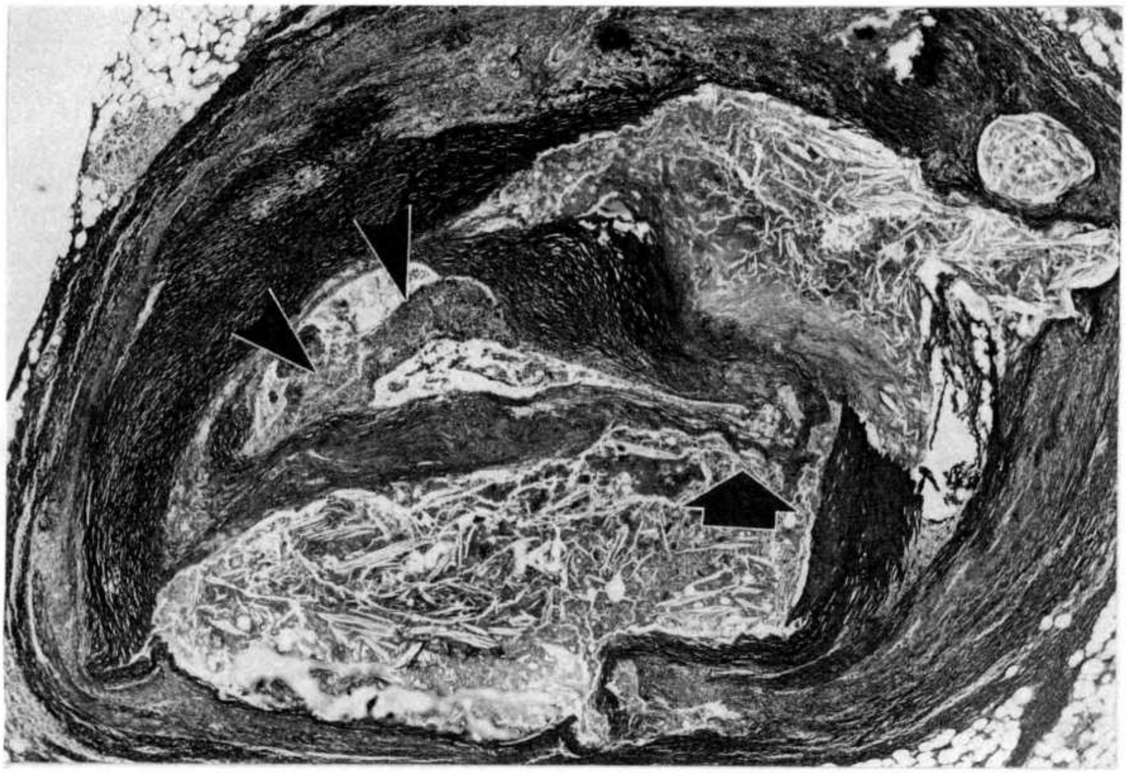


Fig 2 *The left anterior descending coronary artery in patient 7 was stenosed by a ruptured plaque with an intimal lesion (arrow) and resultant lumen thrombus (arrowheads). Martius scarlet blue (original magnification, × 32).*

These thrombi probably originated from the fragmenting proximal obstructive thrombus (fig 4).

Discussion

The potential reduction of myocardial infarct size by thrombolysis and other treatments has been the subject of much interest in recent years.[6] Clinical trials have shown both an improvement in hospital mortality[7] and left ventricular function[8] after intravenous streptokinase treatment. Histopathological evidence of myocardial salvage after coronary reperfusion has mainly come from experimental coronary reperfusion in dogs[9 10] and there has been relatively little published work in human beings. This experimental work has shown that a wavefront of ischaemic necrosis progresses from subendocardial myocardium to subepicardial myocardium over a

Table 3 *Macroscopic and histopathological results*

			Infarct				
Case no	*Infarct site*	*Patency**	*Area (cm²)*	*CN*	*CBN*	*HI*	*Thickness†*
1	A	+	35	+	+	+	Partial
2	A	+	46	+	+	+	Partial
3	A	+	42	+	+	+	Transmural
4	A/I	+	15/6	+	−	−	Partial
5	A	+	40	+	+ +	+	Mixed
6	A	−	56	+	−	+	Transmural
7	A	−	64	+ +	+	+	Transmural
8	I	−	18	+	+ +	−	Partial

*Patency of the infarct artery (+, open; −, closed).
†Extent of myocardial wall necrosis.
CN, coagulative necrosis; CBN, contraction band necrosis; HI, haemorrhagic infarction (+, haemorrhage present).

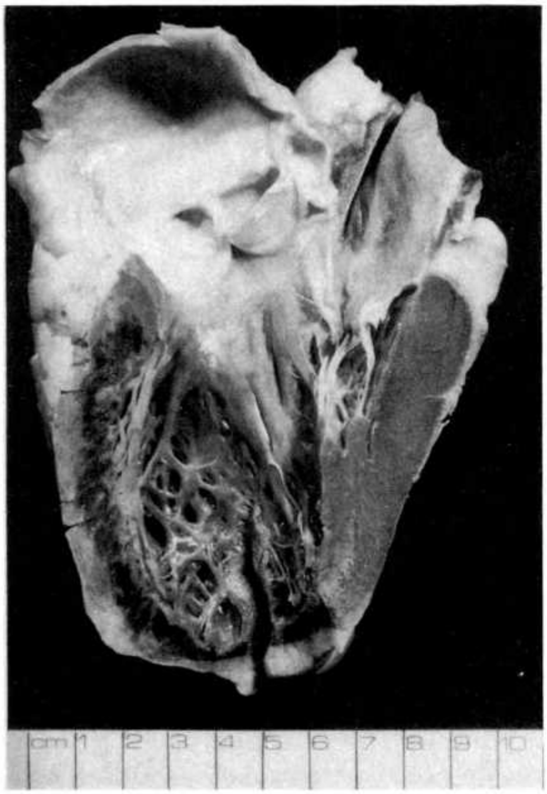


Fig 3 *A case of successful reperfusion in patient 1. The infarct was noticeably haemorrhagic and of partial wall thickness.*

period of several hours. Coronary reperfusion after release of the arterial ligatures halted the progression of this ischaemic wavefront, with salvage of the subepicardial myocardium. The extent of myocardial necrosis was related to the duration of coronary occlusion.

The results of the present study showed a trend towards the occurrence of partial thickness infarction in patients with an open infarct related coronary artery, and transmural infarction in patients with a closed infarct related coronary artery. None the less, we cannot reach any direct conclusions about myocardial salvage after streptokinase treatment. The number of cases examined was small and neither the degree of collateral circulation nor the size of the infarct bed at risk could be adequately assessed. Rentrop *et al* reported on 10 patients who had aortocoronary bypass grafting after intracoronary streptokinase treatment.[11] Intraoperative inspection showed that the bulk of the reperfused myocardium was viable, and biopsy specimens from three patients showed damage only in the subendocardial region.

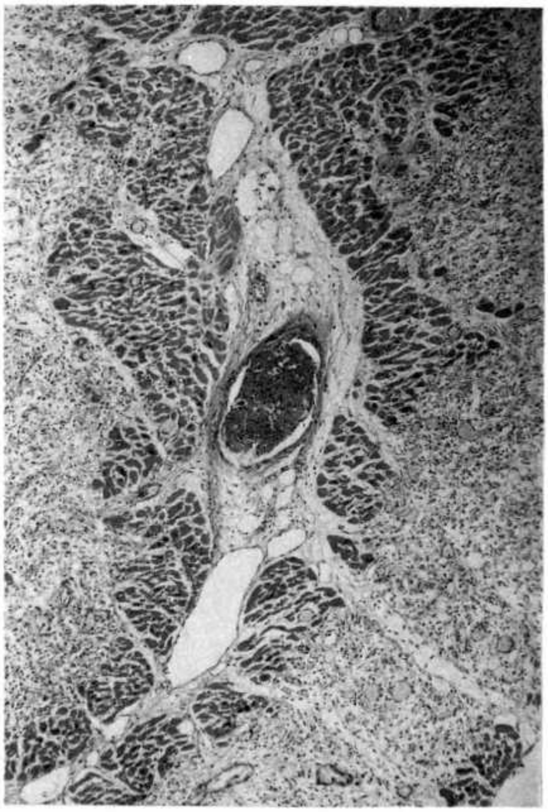


Fig 4 *A surviving zone of perivascular myofibres. The central intramyocardial vessel contained a small embolic thrombus originating from the proximal fragmenting occlusion. Haematoxylin and eosin (original magnification, × 96).*

In partial thickness myocardial infarcts Mattfeldt *et al* described the presence of contraction band necrosis due to aggregation of myofibre sarcomeres caused by reperfusion of irreversibly damaged myocytes.[3] This is different from the usual coagulative necrosis seen in the myocardium after permanent coronary occlusion. Contraction band necrosis was seen in the present study but also occurred in two of the three patients with a persistently occluded infarct related coronary artery as well as in four of the five patients with an open infarct related coronary artery. This suggests that contraction band necrosis is not solely a consequence of myocardial reperfusion.

The success of coronary artery recanalisation has been related to the complexity of the atheromatous occlusion.[3] In this study, four of the five patients with a patent infarct related coronary artery had a simple fibrofatty plaque. In the fifth patient a simple lesion may have been complicated by postinfarction coronary angioplasty. In contrast, a complicated atheromatous stenosis with an acute intimal lesion was shown in all three patients with persistent coronary artery occlusion. This suggests that thrombus associated with a non-complicated lesion may be more easily lysed than thrombus overlying a complex mural lesion. The ease of clot dissolution, however, may also be related to the degree of atheromatous stenosis, which was greater in the complex lesions.

Terrosu *et al* studied the angiographic appearance of the coronary arteries during successful thrombolytic treatment.[12] They found that total coronary occlusion was followed by the restoration of blood flow but with intraluminal filling defects and delayed distal flow possibly due to microembolism. We found intramyocardial microembolism in two of our patients. It is possible that microembolism may limit the benefits of thrombolysis by reducing blood flow through the distal coronary circulation.

The association between streptokinase treatment and haemorrhagic myocardial infarction has previously been noted and has even been held to be responsible for myocardial rupture.[1 2] Haemorrhagic infarction was seen in six of our patients. Haemorrhage occurred into areas of myocardial necrosis and did not extend beyond the infarct into viable myocardium. The presence of infarct haemorrhage was not obviously responsible for complications in our study. This supports the results of experimental studies in dogs. These indicated that reperfusion haemorrhage occurs as a result of the microvascular damage that follows and it is never greater than the extent of myocardial necrosis.[13 14] Whether myocardial haemorrhage has any long term deleterious clinical effects remains uncertain. One encouraging report has shown that collagen formation is not delayed in haemorrhagic reperfused myocardial infarcts in dogs.[15]

Swelling, degeneration, and separation of endothelial cells may lead to microvascular obstruction and the "no-reflow" effect after reperfusion.[16] This may have been important in patient 3 who had a transmural infarct despite a patent infarct related coronary artery.

Myocardial haemorrhage was common after coronary reperfusion but occurred into areas of already irreversibly damaged myocardium and did not contribute to the death of any patient. The success of coronary artery reperfusion may be related to the complexity and degree of the underlying atheromatous lesion.

References

1 Mathey DG, Schofer J, Kuck K-H, Beil U, Kloppel G. Transmural, haemorrhagic myocardial infarction after intracoronary streptokinase. Clinical, angiographic, and necropsy findings. *Br Heart J* 1982;48: 546–51.

2 Yasuno M, Endo S, Takahashi M, *et al.* Angiographic and pathologic evidence of haemorrhage into the myocardium after coronary reperfusion. *Angiology* 1984;35:797–801.

3 Mattfeldt T, Schwarz F, Schuler G, Hofmann M, Kubler W. Necropsy evaluation in seven patients with evolving acute myocardial infarction treated with thrombolytic therapy. *Am J Cardiol* 1984; 54:530–4.

4 Peel AAF, Semple T, Wang I, Lancaster WM, Dall JLG. A coronary prognostic index for grading the severity of infarction. *Br Heart J* 1962;24:745–60.

5 Falk E. Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis. Characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi. *Br Heart J* 1983;50:127–34.

6 Kubler W, Doorey A. Reduction of infarct size. An attractive concept: useful—or possible—in humans? *Br Heart J* 1985;53:5–8.

7 Gruppo Italiano per lo Studio della streptochinasi nell'infarto miocardico. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;i:397–401.

8 The ISAM Study Group. A prospective trial of intravenous streptokinase in acute myocardial infarction (ISAM). Mortality, morbidity, and infarct size at 21 days. *N Engl J Med* 1986;314:1465–71.

9 Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischaemic cell death 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 1977;56:786–94.

10 Jennings RB, Reimer KA. Factors involved in salvaging ischaemic myocardium. effect of reperfusion of arterial blood. *Circulation* 1983;68(suppl I):25–36.

11 Rentrop P, Blanke H, Karsch KR, *et al.* Effects of nonsurgical coronary reperfusion on the left ventricle in human subjects compared with conventional treatment. Study of 18 patients with acute myocardial infarction treated with intracoronary infusion of streptokinase. *Am J Cardiol* 1982;49:1–8.

12 Terrosu P, Ibba GV, Contini GM, Franceschino V. Angiographic features of the coronary arteries during intracoronary thrombolysis. *Br Heart J* 1984;52. 154–63.

13 Kloner RA, Rude RE, Carlson N, Maroko PR, DeBoer LWV, Braunwald E. Ultrastructural evidence of microvascular damage and myocardial cell injury after coronary artery occlusion: which comes first? *Circulation* 1980;62:945–52

14 Fishbein MC, Y-Rit J, Lando Y, Kanmatsuse K, Mercier JC, Ganz W. The relationship of vascular injury and myocardial haemorrhage to necrosis after reperfusion *Circulation* 1980;62:1274–9

15 Roberts CS, Schoen FJ, Kloner RA. Effect of coronary reperfusion on myocardial haemorrhage and infarct healing. *Am J Cardiol* 1983;52:610–4.

16 Hellstrom HR. Coronary artery stasis after induced myocardial infarction in the dog. *Cardiovasc Res* 1971;5:371–5.

Br Heart J 1989;61:396–402

Favourable long term prognosis in patients with non-Q wave acute myocardial infarction not associated with specific electrocardiographic changes

WILLIAM E BODEN,* ROBERT E KLEIGER,† ROBERT S GIBSON,‡
B RAMESH REDDY,* KENNETH B SCHECHTMAN,† DAVID J SCHWARTZ,†
ROBERT J CAPONE,§ ROBERT ROBERTS,¶ and the
DILTIAZEM REINFARCTION STUDY RESEARCH GROUP

*From the *Division of Cardiology and Department of Internal Medicine, Harper Hospital/The Detroit Medical Center and Wayne State University School of Medicine, Detroit, Michigan; †Jewish Hospital, Washington University, St Louis, Missouri; ‡University of Virginia Medical Center, Charlottesville, Virginia; §Rhode Island Hospital, Brown University, Providence, Rhode Island; and ¶Methodist Hospital, Baylor University, Houston, Texas, USA*

SUMMARY Electrocardiograms obtained serially from 544 patients with non-Q wave infarction in the Diltiazem Reinfarction Study were analysed to compare the short term ($\leq$14 days) and long term (one year) follow up of 105 patients (19%) whose admission electrocardiogram showed no localisable repolarisation abnormalities (group 1) with the outcome in 439 patients (81%) who had ST-T wave abnormalities (group 2) localised to two or more contiguous leads within an anterior, inferior, or lateral lead group. There were no major between group differences in baseline clinical variables, concomitant medications, or treatment allocation (diltiazem *v* placebo). Group 2 patients, in the first year, had a higher incidence of early recurrent ischaemia (angina $\geq$24 hours after myocardial infarction associated with ischaemic repolarisation changes), reinfarction, and readmission for chest pain than group 1 patients, despite comparable creatine kinase and creatine kinase MB activities in both groups.

About 20% of patients with acute non-Q wave myocardial infarction did not have definable ST-T wave abnormalities. These patients had a similar clinical and enzymatic profile as patients with non-Q wave infarction with definable ST-T wave abnormalities and they were more likely to have a favourable short term and long term outcome.

Non-Q wave infarction is defined as acute myocardial infarction without the development of new abnormal Q waves. The electrocardiographic changes associated with non-Q wave infarction are typically ST segment shifts or T wave inversions or both that usually persist for at least 48 hours.[1-3] In earlier studies of non-Q wave infarction, ST-T wave abnormalities without subsequent Q wave evolution were required as a key feature of the diagnosis.[4-15] Many patients with acute myocardial infarction confirmed by creatine kinase MB activity do not show Q waves or significant repolarisation changes. The frequency of this finding, however, has not been assessed previously.

We recently reported that both the short term[16] and long term[17] outcomes (death and reinfarction) of patients recovering from acute non-Q wave infarction who had angina associated with ischaemic electrocardiographic changes were significantly worse than in those patients without electrocardiographic changes after infarction. Accordingly, we sought to determine whether the frequency, clinical profile, and prognosis of patients who had isoenzyme confirmed non-Q wave infarction *without* definable ischaemic electrocardiographic changes were different from those with electrocardiographic changes.

We used the extensive data base of the prospective

Requests for reprints to Dr William E Boden, Division of Cardiology, Wayne State University, Harper Hospital, 3990 John R Street, Detroit, MI 48201, USA.

Accepted for publication 20 December 1988

randomised multicentre Diltiazem Reinfarction Study performed in patients with non-Q wave myocardial infarction.[18 19] The objectives of the present study were: (*a*) to define the frequency of non-Q wave infarction without localisation of ischaemic electrocardiographic changes on admission, (*b*) to compare the associated baseline clinical characteristics and enzymatic findings in groups with and without electrocardiographic changes, and (*c*) to compare the early (2–14 day) and late (1 year) outcome variables (post-infarction angina, reinfarction, death) in patients with and without definable acute electrocardiographic changes on admission.

Patients and methods

Five hundred and seventy six patients were randomly assigned to receive diltiazem (360 mg/day) or an equivalent placebo within 72 hours of the development of an enzymatically confirmed non-Q wave infarction. The details of the protocol for this multicentre, double blind, randomised trial (Diltiazem Reinfarction Study) have been reported.[18] In brief, the purpose of this trial was to assess whether the prophylactic administration of high dose diltiazem during the early course of non-Q wave myocardial infarction prevented early recurrent infarction (extension) within the first 14 days of hospital admission. Recurrent infarction was defined as a secondary rise in the plasma activity of creatine kinase MB which was analysed every 12 hours throughout hospital stay.

ELECTROCARDIOGRAPHIC RECORDINGS AND INTERPRETATIONS

The initial diagnosis of acute myocardial infarction was confirmed by serial rises in *both* serum or plasma creatine kinase and creatine kinase MB, according to the laboratory standards for each participating hospital. The electrocardiographic criteria were absence of abnormal Q waves (0·03 second in duration) in ≥ 2 leads within a given lead group or absence of R waves ($\geq 0{\cdot}04$ second in lead V1 and an R:S ≥ 1 in lead V2).

Unlike previous studies, acute ST segment displacement and T wave inversions were not absolute prerequisites for entry into the study. Significant ST segment shifts were defined as the presence of at least 1 mm of ST segment elevation or depression, or T wave inversion in at least two leads within a given infarct location: anterior = leads V1 to V4; lateral = leads I, aVL, V5, and V6; inferior = leads II, III, and aVF. Criteria for posterior non-Q wave infarction could not be established because concomitant anterior ST segment depression in leads V1 to V4 indicative of "anterior" nontransmural infarction interfered with this electrocardiographic interpretation of early evolving posterior infarction. If there was left ventricular hypertrophy, 2 mm ST segment displacement was needed to establish the site of non-Q wave infarction. For electrocardiographic localisation of a non-Q wave infarction we needed to see changes in at least two leads within one of the three infarct locations (anterior, lateral, or inferior).

The sequential electrocardiograms of all study patients on entry, day 2, day 3, and before discharge were scored and forwarded to the electrocardiographic committee, which consisted of five investigators who were blinded to all clinical information. A total of 2 304 electrocardiograms were analysed and entered into a computerised data bank. All data were stored on the Washington University School of Medicine IBM mainframe computer system and were analysed by the Statistical Analysis System.[20 21]

CLINICAL AND LABORATORY EVALUATION

After randomisation, the following evaluations were performed: (*a*) daily clinical evaluation by the investigator; (*b*) electrocardiogram at the time of recurrent pain and for a minimum of three consecutive days if reinfarction was suspected; and (*c*) serial blood samples for analysis of total creatine kinase and creatine kinase MB activity. All protocol samples were sent to the creatine kinase core laboratory for measurement of plasma isoenzyme activity by the batch absorption glass bead method.[22 23] An initial sample was taken at the time of randomisation and samples were drawn every 12 hours thereafter throughout the 14 day study.

DEFINITION OF END POINTS

The primary end point of the Diltiazem Reinfarction Study was reinfarction during the first 14 days after onset of acute non-Q wave infarction. This was defined as an increase of $\geq 50\%$ above baseline in the plasma activity of creatine kinase MB in at least two samples taken at least six hours apart over 24 hours, with an absolute value ≥ 15 μkat/l in at least one sample.

Patients in the Diltiazem Reinfarction Study were followed up by telephone questionnaire of the referring physicians and patient's family. Follow up end points included death, reinfarction, readmission to hospital with recurrent angina, myocardial revascularisation (coronary bypass surgery or percutaneous transluminal coronary angioplasty), or any combination of one or more above cardiovascular events. Follow up was achieved in 535 study participants (91%) and all outcome variables were assessed one year after admission with non-Q wave infarction.

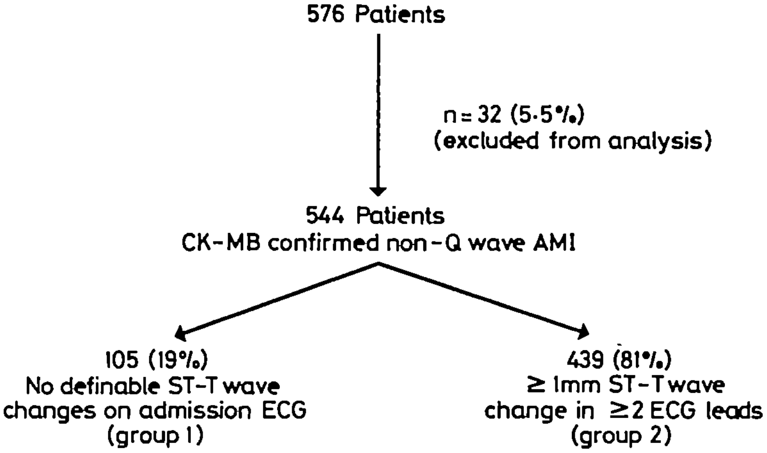


Fig 1 *Flow diagram of admission electrocardiographic findings of Diltiazem Reinfarction Study population (see text for description of electrocardiographic criteria). AMI, acute myocardial infarction; ECG, electrocardiogram.*

STATISTICAL ANALYSIS

Continuous data are expressed as mean (SD). Fourteen day and one year event rates for reinfarction confirmed by creatine kinase MB activity and for death were analysed in the group with ischaemic electrocardiographic changes and the group without. Comparisons between groups were made by *t* tests or the appropriate non-parametric test for continuous variables and Fisher's exact test for discrete variables. A Kaplan-Meier survivorship curve was generated by the LIFETEST procedure of the Statistical Analysis System,[20,21] and one year survival curves were compared by the generalised Wilcoxon test.

Results

CLINICAL CHARACTERISTICS

Thirty two (5·5%) of the 576 patients had evidence of a Q wave myocardial infarction at randomisation (fig 1). These patients were excluded from subsequent analysis. A hundred and five (19·3%) of the remaining 544 study patients with isoenzyme-confirmed non-Q wave infarction had no definable ischaemic changes on the admission electrocardiogram (group 1). The remainder (439 patients (80·7%)) had definable ST-T wave abnormalities on the entry electrocardiogram (group 2). Most of the baseline clinical variables including age, sex, previous myocardial infarction, Killip Class, and blinded treatment assignment were similar in these two groups (table 1). Cigarette smoking was significantly more common in group 2 (57%) than in group 1 (46%).

ENZYMATIC FINDINGS

Total mean peak creatine kinase and creatine kinase MB values were assessed for all 544 patients according to the electrocardiographic site of non-Q wave infarction. These subgroup comparisons were based on the location of the repolarisation changes from the qualifying electrocardiogram (table 2). There were no significant differences, although mean total creatine kinase activity was highest in group 1 patients with non-localisable non-Q wave myocardial infarction. Thus even when there were no or non-diagnostic repolarisation changes patients had the same enzymatic findings of myocardial necrosis as those seen in patients with anterior or multiple location non-Q wave infarctions. The mean creatine

Table 1 *Baseline characteristics of the two study groups*

Characteristic	*Group 1 (n = 105)*	*Group 2 (n = 439)*
Age (yr) (mean (SD))	60 (10)	61 (10)
Male (%)	82	77
Obesity (%)	20	21
Cigarette smoking (%)	46	57*
Diabetes mellitus (%)	24	26
Hypertension (%)	42	42
Left ventricular hypertrophy (%)	26	23
Previous AMI (%)	43	42
Previous CABG/PTCA (%)	9	13
Previous CHF (%)	4	7
Killip class		
Class I (%)	79	79
Class II (%)	15	16
Class III (%)	5	6

*p < 0 05, group 1 *v* group 2.
AMI, acute myocardial infarction; CABG, coronary artery bypass graft surgery; CHF, congestive heart failure, PTCA, percutaneous transluminal coronary angioplasty.

Table 2 *Peak creatine kinase and creatine kinase MB activities (IU/l) according to electrocardiographic location of non-Q wave acute myocardial infarction based on analysis of admission tracing (mean (SD))*

Enzyme	*Combination* *(≥2 locations)*	*Lateral* *(I, aVL, V5–V6)*	*Anterior* *(V1–V4)*	*Inferior* *(II, III aVF)*	*Non-localisable* *(no ST-T change)*
CK (IU)	641 (577)	560 (435)	646 (683)	611 (529)	668 (877)
CK MB (IU)	21 (37)	27 (42)	37 (91)	12 (13)	22 (36)

CK, creatine kinase; MB, myocardial band.
p = NS among subgroups by analysis of variance

kinase and creatine kinase MB values for group 1 patients were 10·7 (14·0) μkat/l (668 (877) IU/l) and 0·22 (0·36) μkat/l (22 (36) IU/l) and for group 2 patients were 10 (9·0) μkat/l (625 (562) IU/l) and 0·24 (0·44) μkat/l 24 (44) IU) respectively (p = NS).

SHORT TERM AND ONE YEAR OUTCOME

Twenty one per cent of group 2 patients (93/439) and only 12% of group 1 patients (13/105) had post-infarction angina associated with transient ST-T wave abnormalities before discharge (≤14 days) indicative of early recurrent ischaemia (p = 0·040). Reinfarction occurred within 14 days of infarction in 6·6% of group 2 patients (29/439) and in 10·4% of group 1 patients (11/105) (p = 0·172). There were 20 deaths within 14 days of non-Q wave myocardial infarction: 15 in group 2 patients and five in group 1 patients (p = NS).

At one year follow up, 15% of group 2 patients had died (67/439) compared with 8% of group 1 patients (7/105) (p = 0·021) (fig 2). Moreover, 17% of group 2 patients (75/439) developed late recurrent infarction between hospital discharge and one year (17%), compared with 10% of group 1 patients (11/105) (p = 0·043).

Finally, an additional 27% of group 2 patients were readmitted for chest pain during the one year follow up, compared with 20% of group 1 patients (p = 0 056).

Discussion

Our results show that approximately 20% of all patients admitted to the coronary care unit with acute non-Q wave myocardial infarction have non-localisable electrocardiographic changes, despite raised

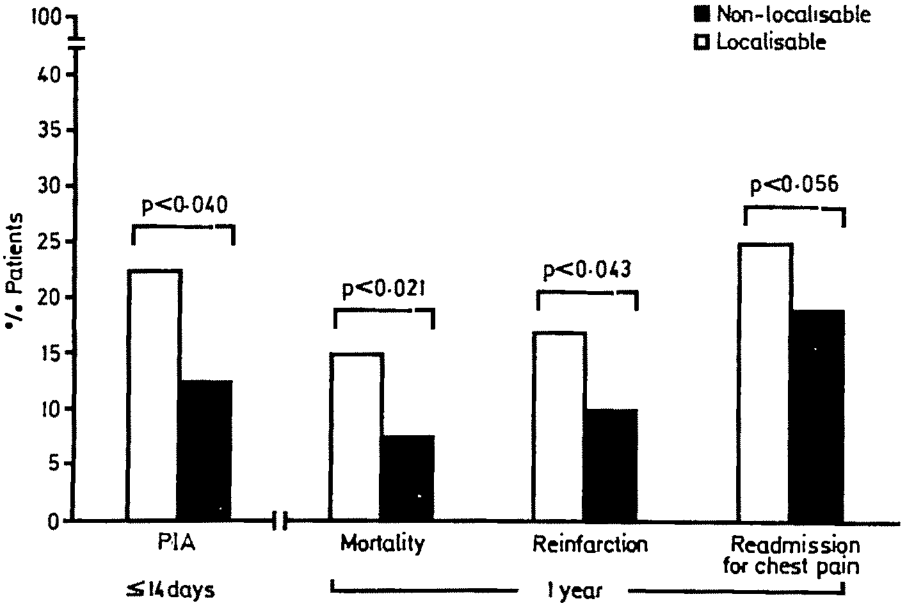


Fig 2 *Outcome variables (post-infarction angina (PIA) with transient electrocardiographic changes before hospital discharge, mortality, and reinfarction during one year follow up) for the group of patients with non-Q wave AMI and non-localisable ST-T wave changes and the group of patients with localisable repolarisation abnormalities.*

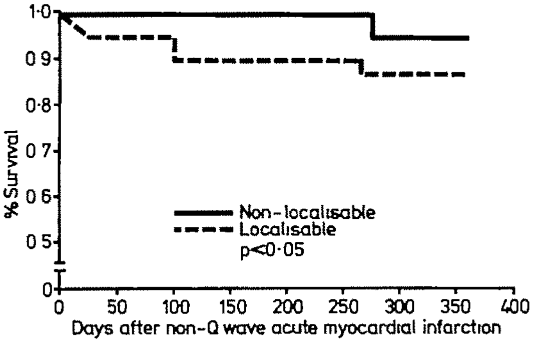


Fig 3 *Kaplan-Meier survivorship curve for one year mortality in patients with non-localisable electrocardiographic changes and localisable ST-T wave changes.*

activity of plasma total creatine kinase and creatine kinase MB. Early recurrent ischaemia, death within a year of infarction, reinfarction, and readmissions for chest pain were significantly less common in patients without definable ST-T wave abnormalities than in those with.

We found that patients with early post-infarction angina were at increased risk of reinfarction and death during the first two weeks after non-Q wave myocardial infarction,[16] and that angina associated with transient ischaemic electrocardiographic changes identified a subset at particularly high risk. In the subgroup of patients with non-Q wave infarction and electrocardiographic evidence of ischaemia reinfarction was four times more common and the mortality rate within 14 days of randomisation was ten times higher than in patients without early recurrent myocardial ischaemia.[16] We recently extended the period of observation to one year and we confirmed that the presence of post-infarction angina with ischaemic electrocardiographic changes during the hospital stay was a potent predictor of subsequent cardiac events; in these patients mortality and non-fatal reinfarction were significantly increased during the one year follow up.[17]

In the context of our recent observations that ischaemic electrocardiographic changes complicating non-Q wave infarction are a harbinger of adverse short term[16] and long term[17] outcome, the findings in our present report provide important complementary evidence that the *absence* of definable early ST-T wave changes in non-Q wave myocardial infarction characterised a subgroup of patients in whom the risk for late reinfarction and mortality is lower than in those with localisable repolarisation abnormalities. There were no significant differences in peak total creatine kinase or creatine kinase MB values among subgroups with and without electrocardiographic changes, even in those patients who showed "global" (anterior + inferior + lateral) electrocardiographic changes. Thus the generally more favourable outcome of non-Q wave infarction patients without definable acute electrocardiographic changes could not be explained on the basis of a smaller infarct.

The pathophysiological basis of why almost a fifth of all non-Q wave infarction patients have "electrocardiographically silent" myocardial necrosis was not investigated in the Diltiazem Reinfarction Study. Our findings have several possible explanations. First, when infarction in left ventricular segments is associated with electrocardiographic changes that are electrically opposite in the same plane (anterior-posterior; inferior-lateral) or reciprocal in perpendicular planes (anterior-inferior) the opposing vector forces may cancel out, resulting in a net absence of discernible electrocardiographic findings.[24-26]

Secondly, whereas the process of ventricular depolarisation (phase O) is rapid and attended by a reasonably uniform potential difference across the boundary of activation,[27] repolarisation is considerably longer and non-uniform (phases 2 and 3) and is characterised by differing potentials across various boundaries.[28] Experimentally, the magnitude of T wave changes, unlike that of the QRS complex, has been shown to be unrelated to the mass of myocardium infarcted.[29] Thus patchy areas of necrosis may produce differential regions of repolarisation, resulting in the genesis of non-uniform, absent, or non-specific T waves.[29]

Thirdly, infarction of the posterior wall (or basal lateral segments) of the left ventricle may not be detected with the 12 lead scalar electrocardiogram. This is the last area to be depolarised, and necrosis of this area would affect only the terminal 0·04 to 0·06 second of the QRS complex.[30-32] Such posterior or high lateral infarctions, characteristic of occlusions of the left circumflex or obtuse marginal branch coronary arteries, may be attended by few, if any, electrocardiographic changes.[33 34]

Thus certain patients without definable repolarisation changes could have occult "transmural" infarctions that simply escape electrocardiographic detection. Our observations that this group had higher early peak creatine kinase values, but lower one year mortality and reinfarction rates, support the hypothesis that such patients had "completed" infarctions with less (but certainly not absent) residual myocardial ischaemia.

In summary, there appear to be important prognostic differences between patients with non-Q wave infarction who have definable ST-T wave abnormalities and those who do not; patients without localisable ischaemic repolarisation changes fared better in the short term and long term than patients with non-Q wave infarction and demonstrable electrocardiographic abnormalities on admission. Nevertheless, rates of early recurrent ischaemia (12%), early reinfarction (10%), and mortality in the first year (8%) were by no means negligible in those without electrocardiographic changes.

Risk stratification techniques can identify subgroups of patients at high risk after infarction who may benefit from additional diagnostic evaluation and more vigorous management.[35,36] Our observations suggest that approximately 20% of patients with non-Q wave myocardial infarction without definable ST-T wave abnormalities are at lower risk and, in the absence of recurrent ischaemic symptoms, may not need the same type of urgent diagnostic/therapeutic intervention before hospital discharge as most other subgroups of patients with non-Q wave infarction. Accordingly, we feel it is appropriate to recommend continuing medical treatment in such patients who are otherwise clinically stable, although regular, careful examinations after infarction would be prudent.

References

1 Cook RW, Edwards JE, Pruitt RD. Electrocardiographic changes in acute subendocardial infarction. I. Large subendocardial and large nontransmural infarcts. *Circulation* 1958;**18**:603–9.

2 Cook RW, Edwards JE, Pruitt RD. Electrocardiographic changes in acute subendocardial infarction II. Small subendocardial infarcts *Circulation* 1958;**18**:613–21.

3 Mills RM, Young E, Gorlin R, Lesch M. Natural history of S-T segment elevation after acute myocardial infarction. *Am J Cardiol* 1975;**35**:609–18.

4 Scheinman MM, Abbott JA. Clinical significance of transmural versus nontransmural electrocardiographic changes in patients with acute myocardial infarction. *Am J Med* 1973;**55**:502–11.

5 Rigo P, Murray M, Taylor DR, Weisfeldt ML, Strauss HW, Pitt B. Hemodynamic and prognostic findings in patients with transmural and nontransmural infarction. *Circulation* 1975;**51**:1064–73

6 Cannon DS, Levy W, Cohen LS. The short and long-term prognosis of patients with transmural and nontransmural myocardial infarction. *Am J Med* 1976;**61**:452–9.

7 Szklo M, Goldberg R, Kennedy HL, Tonascia JA Survival of patients with nontransmural myocardial infarction: a population based study. *Am J Cardiol* 1978;**42**:648–54.

8 Ahmed SS, Brancato RR. Transmural versus nontransmural myocardial infarction—influence of location on clinical features and mortality. *Angiology* 1979;**30**:240–7.

9 Connolly DC, Elveback LR. Comparison of hospital and post-hospital course of patients with transmural and subendocardial myocardial infarction [Abstract]. *Am J Cardiol* 1979;**43**:370.

10 Fabricius-Bjerre N, Munkvad M, Knudsen JB. Subendocardial and transmural myocardial infarction—a five year survival study. *Am J Med* 1979;**66**:986–91.

11 Boxall J, Saltups A. A comparison of nontransmural and transmural myocardial infarction. *Aust NZ J Med* 1980;**10**:176–82.

12 Mahony C, Hindman MC, Aronin N, Wagner GS Prognostic differences in subgroups of patients with electrocardiographic evidence of subendocardial or transmural myocardial infarction: the favorable outlook for patients with an initially normal QRS complex. *Am J Med* 1980;**69**:1983–7.

13 Thanavaro S, Krone RJ, Kleiger RE, *et al.* In-hospital prognosis of patients with first nontransmural and transmural infarctions. *Circulation* 1980;**61**:29–36.

14 Hutter AM, DeSanctis RW, Flynn T, Yeatman LA. Nontransmural myocardial infarction: a comparison of hospital and late clinical course of patients with that of matched patients with transmural anterior and transmural inferior myocardial infarction. *Am J Cardiol* 1981;**48**:595–601.

15 Krone RJ, Friedman E, Thanavaro S, Miller JP, Kleiger RE, Oliver GC. Long-term prognosis after first Q-wave or non-Q wave myocardial infarction. analysis of 593 patients. *Am J Cardiol* 1983;**52**: 234–40.

16 Gibson RS, Young PM, Boden WE, Schechtmen K, Roberts R. Prognistic significance and beneficial effect of diltiazem on the incidence of early recurrent ischemia after non-Q wave myocardial infarction: results from the Multicenter Diltiazem Reinfarction Study. *Am J Cardiol* 1987;**60**:203–9.

17 Boden WE, Gibson RS, Schechtman KB, Capone RJ, Kleiger RE, The Diltiazem Reinfarction Study (DRS) Group: the prevalence and long-term prognosis of predischarge ST depression following acute non-Q wave myocardial infarction [Abstract]. *Circulation* 1987;**76**(suppl IV):IV–392

18 Gibson RS, Boden WE, Theroux P, *et al.* Diltiazem and reinfarction in patients with non-Q wave myocardial infarction: results of a double-blind, randomized, multicenter trial. *N Engl J Med* 1986;**315**:423–9.

19 Pratt C, Gibson RS, Boden WE, *et al.* The design of a multicentered, double-blind study to assess the effects of prophylactic diltiazem on early reinfarction occurring in patients after non-Q wave infarction: the diltiazem reinfarction study. *Am J Cardiol* 1986; **58**:906–10.

20 *SAS Users Guide*. Basics version. 5th ed. Cary, NC: SAS Institute, 1985:1290.

21 *SAS Users Guide*. Statistics version. 5th ed. Cary, NC. SAS Institute, 1985.956.

22 Henry PD, Roberts R, Sobel BE. Rapid separation of plasma creatine kinase isoenzymes by batch adsorption on glass beads *Clin Chem* 1975,**21**:844–9.

23 Ritter CS, Mumm SR, Roberts R. Improved radioimmunoassay for creatine kinase isoenzymes in plasma. *Clin Chem* 1981;**27**:1878–87.

24 Pruitt RD, Dennis EW, Kinard SA. The difficult electrocardiographic diagnosis of myocardial infarction. *Prog Cardiovasc Dis* 1963;6:85–91.

25 Suguira M, Okada R, Lizuka H. A clinicopathological study on the subendocardial infarction in the aged. *Jpn Heart J* 1969;10:203–10.

26 Horan LG, Flowers NC. Diagnostic power of the Q wave: critical assay of its significance in both detection and localization of myocardial deficit. In: Schlant RC, Hurst JW, eds. *Advances in electrocardiography*. New York: Grune and Stratton, 1972:321.

27 Burgess MJ, Lux RL. Physiologic basis of the T wave. In: Schlant RC, Hurst JW, eds. *Advances in electrocardiography*. New York: Grune and Stratton, 1976:327–37.

28 Abildskov JH. Nonspecificity of ST-T changes. In: Fisch C, ed. *Cardiovascular clinics, complex arrhythmias*. Vol 6. Philadelphia. FA Davis, 1973:170–7

29 Autenrieth G, Surawicz B, Kuo CS, Arita M. Primary T wave abnormalities caused by uniform and regional shortening of ventricular monophasic action potential in the dog. *Circulation* 1975;51:668–76.

30 Perloff JK. The recognition of strictly posterior myocardial infarction by conventional scalar electrocardiography. *Circulation* 1964;30:706–18.

31 Benchimol A, Desser KB. The electrovector-cardiographic diagnosis of posterior wall myocardial infarction. In: Fisch C, ed. *Complex electrocardiography*. Philadelphia: FA Davis, 1973:182–97.

32 Levy L, Jacobs HJ, Chastant HP, Strauss HB. Prominent R wave and shallow S wave in lead V1 as a result of lateral myocardial infarction. *Am Heart J* 1950;40:447–52.

33 Bough EW, Boden WE, Korr KS, Gandsman EJ. Left ventricular asynergy in electrocardiographic "posterior" myocardial infarction. *J Am Coll Cardiol* 1984;4:209–15.

34 Mamby SA, Bradley AB, Boden WE Early precordial S-T segment depression due to isolated acute right or left circumflex coronary artery occlusion: implications for thrombolytic therapy selection. *Am J Cardiol* 1987;60:726–8.

35 Beller GA, Gibson RS. Risk stratification after myocardial infarction. *Mod Concepts Cardiovasc Dis* 1986;55:5–10.

36 O'Rourke RA. Clinical decisions for post myocardial infarction patients *Mod Concepts Cardiovasc Dis* 1986;55:55–60.

Br Heart J 1989;61:403–9

Risk factors for stroke and myocardial infarction in women in the United Kingdom as assessed in general practice: a case-control study

S G THOMPSON,* G GREENBERG,† T W MEADE

From the Medical Research Council Epidemiology and Medical Care Unit, Northwick Park Hospital, Harrow

SUMMARY Data available in the United Kingdom through the Medical Research Council's General Practice Research Framework were recorded in a study of 603 women aged 45–69 with confirmed diagnoses of stroke or myocardial infarction, each matched by age with two controls. Current cigarette smoking and a family history of myocardial infarction were both strongly associated with the risk of stroke and myocardial infarction, with relative risks of 2·47 (95% confidence interval 1·89 to 3·23) and 1·93 (95% confidence interval 1·52 to 2·44) respectively. The relative risks associated with past smoking decreased according to the length of time since stopping smoking. A family history of stroke was not significantly related to the risk of stroke or myocardial infarction. Single women had a lower risk of stroke and myocardial infarction than married women (relative risk 0·49), but parity, past use of oral contraceptives, and menopausal state were not significantly related to the risk of stroke and myocardial infarction in this study. Other characteristics that were identified as risk factors either for subsequent stroke or for myocardial infarction included not only hypertension, diabetes, and past histories of stroke and myocardial infarction, but also past histories of gynaecological cancer and of venous thrombosis. The association with venous thrombosis may indicate the importance of the haemostatic system in a common pathogenesis of venous thrombosis and myocardial infarction.

Most information on population risk factors for stroke and myocardial infarction is based on epidemiological studies of men, whose risk of cardiovascular disease is greater than that of women. Whereas the risks of fatal stroke are fairly similar in men and women, the risk of fatal ischaemic heart disease is substantially lower in women than in men at all ages, especially so under the age of about 65 years. About 40% of deaths in women of all ages and >20% of those in women under the age of 65, however, are attributed to ischaemic heart disease or cerebrovascular disease.[1] Additional information on risk factors for stroke and myocardial infarction in women alone is therefore needed to provide a complete description of the important risk factors in the population as a whole.

In a case-control study of stroke and myocardial infarction in women in the United Kingdom, based in general practice, in which the focus was on the use of menopausal hormonal replacement therapy,[2] information was also systematically collected on other potential risk factors. This paper describes the findings of the study with regard to these other factors.

Patients and methods

The methods have been described in detail elsewhere[2]; only the essential features are reported here. The study was based in 83 practices belonging to the Medical Research Council's General Practice Research Framework.[3] Over a five and a half year period from 1981 to 1986, cases of fatal and non-fatal stroke and myocardial infarction in white women aged 45 to 69 were investigated. Copies of additional

---

*Present address and requests for reprints to Dr S G Thompson, Department of Clinical Epidemiology and General Practice, Royal Free Hospital Medical School, Rowland Hill Street, London NW3 2PF.

†Present address Department of Health, Richmond House, 79 Whitehall, London SW1A 2NS. (The contents of this article represent the author's views alone and do not commit the Department of Health.)

Accepted for publication 16 February 1989

information (such as hospital records and necropsy reports) were sought and the events classified by a single assessor using World Health Organisation criteria.[4,5] For the purposes of statistical analysis, the 84 cases in the "possible" and the 275 cases in the "definite" categories of myocardial infarction were considered together, while suspected cases not meeting the criteria were excluded from the study. Of the total of 244 strokes finally accumulated in the study, 37 (15%) were fatal; 94 (26%) of the 359 myocardial infarctions were fatal.

Two controls were selected for each case. The controls were white women whose ages were within two years of the age of the case and who had the same general practitioner. We selected them by taking the first eligible older and first eligible younger patient working sequentially from the case patient through the age/sex register.

A research nurse in each practice obtained information from the woman (or her next of kin) by interview on marital status, parity (defined in terms of the number of live births), oral contraceptive use, cigarette smoking habit, family history of stroke or myocardial infarction, and menopausal state. Current smokers included women who had given up smoking in the same year as the case's stroke or myocardial infarction. A positive family history of stroke was recorded if the woman's father, mother, or any brother or sister had suffered a non-fatal or fatal stroke. A family history of myocardial infarction was similarly defined. A woman was classified as premenopausal if she was still menstruating, whether regularly or not. For a proportion of cases with a fatal event, some of these items of information were not available. Information on the medical history of all the women was taken from the medical notes and was thus complete.

Specially trained quality control nurses travelled to each of the 83 practices to check the procedure for selecting controls. Also, for 90 women in the study (two women in each of about half of the practices), the quality control nurse independently repeated the abstracting of the information on medical history from the medical notes. Discrepancies between the two nurses were most common for the past history of hypertension—in seven the quality control nurse recorded hypertension and the practice nurse did not, and the converse for eight. Of a total of 14 discrepancies, seven each for the past history of stroke and myocardial infarction, there were ten in which the quality control nurse recorded a positive history and the practice nurse did not, and the converse for four.

The relative risks of stroke and myocardial infarction were estimated by conditional maximum likelihood logistic regression[6] appropriate for matched case-control studies. The p values quoted are two sided and are given exactly for values between 0·2 and 0·001.

Results

The risk of stroke and myocardial infarction was lower for single women than for married women (relative risk 0·49, table 1). The relative risks of stroke and myocardial infarction separately according to marital state were not dissimilar ($p > 0·2$). The 17% of women who were nulliparous had a similar risk of stroke and myocardial infarction compared with parous women, the relative risk being 0·80 ($p = 0·15$) when unadjusted and 1·02 ($p > 0·2$) when adjusted for marital status.

Only two women were current users of oral contraceptives, that is at the time of stroke or myocardial infarction in the case. Of all the women, 9% had used oral contraceptives in the past. The average time since last use was 11 years. This use of oral contraceptives was not associated with the risk of stroke and myocardial infarction (relative risk 0·73, $p = 0·16$). The 6% of women classified as premenopausal did not have a significantly lower risk of stroke and myocardial infarction than postmenopausal women (relative risk 0·91, $p > 0·2$).

The risk of stroke and myocardial infarction was

Table 1 *Numbers of cases and controls according to marital state and estimates of relative risks of stroke and myocardial infarction*

Marital state	*Numbers (%) of.*		*Relative risk**		
	Cases	*Controls*	*Stroke and MI (95% confidence interval)*	*Stroke alone*	*MI alone*
Married	431 (74)	869 (72)	1	1	1
Single	22 (4)	85 (7)	0·49 (0·30, 0·82)	0·48	0·50
Widowed	107 (18)	201 (17)	1·08 (0·81, 1·42)	1·16	1·01
Divorced or separated	19 (3)	51 (4)	0·82 (0·45, 1·47)	0·92	0·76

MI, myocardial infarction.

*Relative risks, relative to married women, take into account the matched design of the study The relative risks for stroke and myocardial infarction combined are significantly different between the four categories of marital status ($p = 0·02$).

Table 2 *Numbers of cases and controls and estimates of relative risk of stroke and myocardial infarction according to stated cigarette smoking habit and time since giving up in ex-smokers*

Cigarette smoking habit	*Numbers (%) of.* *Cases*	*Numbers (%) of.* *Controls*	*Relative risk** *Stroke and MI (95% confidence interval)*	*Relative risk** *Stroke alone*	*Relative risk** *MI alone*
Life-long non-smokers	155 (33)	556 (46)	1	1	1
All current smokers	217 (46)	308 (26)	2·47 (1·89, 3·23)	2·26	2·63
All ex-smokers	104 (22)	339 (28)	1·10 (0·81, 1·49)	1·11	1·08
According to time (yr) since giving up.†					
1– 2	23	41	1·85	1·86	1·85
3– 5	16	42	1·60	1·56	1·61
6–10	18	58	1·37	1·66	1·18
11–15	13	45	0·99	1·02	0·95
>15	34	153	0·72	0·79	0·66
Total	476 (100)	1203 (100)			

MI, myocardial infarction.

*Relative risks, relative to life-long non-smokers, take into account the matched design of the study.

†p Value for trend according to time since giving up for stroke and myocardial infarction combined, $p = 0·001$. There was no significant difference ($p > 0·2$) between the trends for stroke and myocardial infarction

higher in current cigarette smokers than in those who had never smoked (relative risk 2·47, $p < 0·001$, table 2). The relative risks for stroke and myocardial infarction separately were similar (2·26 and 2·63 respectively). There was a suggestion that the relative risks decreased with age (test for trend, $p = 0·08$), with the relative risks in the five year age groups from 45 to 69 being 3·7, 5·7, 2·5, 2·3, and 2·0. Ex-smokers of cigarettes did not have an increased risk of stroke and myocardial infarction overall, but there was a gradient of risk according to the time since giving up smoking (table 2) such that the risk was highest in those who had given up most recently. The gradients of risk were very similar for each of stroke and myocardial infarction separately (table 2).

A family history of myocardial infarction was associated with the risk of stroke and myocardial infarction (relative risk 1·93, $p < 0·001$) but a family history of stroke was not (relative risk 1·10, $p > 0·2$, table 3). There was no evidence that a positive family history of one type of event (that is, stroke or myocardial infarction) related in particular to the risk of that type of event (table 3).

Table 4 shows the risks of stroke and myocardial infarction associated with the medical histories recorded. The relative risk was particularly high for past histories of stroke or subarachnoid haemorrhage, myocardial infarction, and diabetes. Past histories of stroke or subarachnoid haemorrhage and of hypertension were more strongly related to the subsequent risk of stroke than to the risk of myocardial infarction, the corresponding relative risks (table 4) being significantly different ($p = 0·005$ and $p = 0·03$ respectively). Past histories of myocardial infarction and of diabetes were similarly related to the subsequent risk of stroke and of myocardial infarction (both $p > 0·2$ for a difference in relative risks). Though a past history of venous thrombosis did not seem important in the subsequent risk of stroke, it was related to the subsequent risk of myocardial infarction; the relative risk of 3·78 for subsequent myocardial infarction was significantly greater ($p = 0·01$) than that for stroke (1·16, table 4). A past history of cancer (endometrial, ovarian,

Table 3 *Numbers of cases and controls with a family history of stroke or myocardial infarction in any first degree relative and estimates of relative risks of stroke and myocardial infarction*

Family history of	*Risk of stroke and/or MI*	*Numbers (%) of:* *Cases*	*Numbers (%) of:* *Controls*	*Relative risk* (95% confidence interval)*
Stroke	S	76 (40)	163 (33)	1·33 (0·93, 1·92)
	MI	90 (35)	253 (35)	0·95 (0·69, 1·31)
	S + MI	166 (37)	416 (35)	1·10 (0·87, 1·40)
Myocardial infarction	S	88 (46)	156 (32)	1·85 (1·28, 2·66)
	MI	142 (55)	268 (38)	1·99 (1·46, 2·70)
	S + MI	230 (51)	424 (35)	1·93 (1·52, 2·44)

S, stroke, MI, myocardial infarction

*Relative risks, relative to the group of women without the corresponding family history; these take into account the matched design of the study.

Table 4 *Numbers of cases and controls with a recorded past history of various diseases and estimates of relative risk of stroke and myocardial infarction*

Past history of:	*Risk of stroke and/or MI*	*Numbers (%) of:* Cases	Controls	*Relative risk* (95% confidence interval)*
Stroke and subarachnoid haemorrhage	S	57 (23)	9 (2)	14·1 (6·61, 30·0)
	MI	8 (2)	7 (1)	2·29 (0·81, 6·43)
	S + MI	65 (11)	16 (1)	8·57 (4·83, 15·2)
Hypertension (excluding in pregnancy)	S	155 (64)	111 (23)	6·09 (4·15, 8·95)
	MI	190 (53)	186 (26)	3·53 (2·61, 4·76)
	S + MI	345 (57)	297 (25)	4·41 (3·48, 5·58)
Myocardial infarction	S	17 (7)	2 (<1)	17·0 (3·81, 75·8)
	MI	69 (19)	8 (1)	19·5 (8·82, 43·1)
	S + MI	86 (14)	10 (1)	19·0 (9·40, 38·2)
Diabetes	S	27 (11)	6 (1)	10·5 (3·97, 27·9)
	MI	37 (10)	10 (1)	9·96 (4·36, 22·8)
	S + MI	64 (11)	16 (1)	10·2 (5·42, 19·1)
Venous thrombosis	S	15 (6)	26 (5)	1·16 (0·60, 2·23)
	MI	29 (8)	16 (2)	3·78 (2·00, 7·15)
	S + MI	44 (7)	42 (3)	2·14 (1·38, 3·32)
Arterial thrombosis (other than stroke, SAH, or MI)†	S + MI	19 (3)	9 (1)	4·22 (1·88, 9·48)
Cancer‡	S	10 (4)	27 (6)	0·73 (0·35, 1·56)
	MI	19 (5)	17 (2)	2·24 (1·15, 4·36)
	S + MI	29 (5)	44 (4)	1·32 (0·82, 2·14)

S, stroke; MI, myocardial infarction; SAH, subarachnoid haemorrhage.

*Relative risks, relative to the group of women without a past history of the corresponding disease; these take into account the matched design of the study. All the relative risks (for stroke + MI together) are statistically highly significant ($p < 0·001$), except for the four cancers ($p > 0·2$).

†Too few for subdivision.

‡Endometrial, ovarian, cervical, or breast cancer.

cervical, or breast) was significantly related to the risk of myocardial infarction, but not to the risk of stroke (table 4).

When all the medical histories were considered simultaneously in a multivariate analysis, the estimated relative risks were generally slightly less than those presented in table 4 because of the interrelations between them. While the risk associated with a past history of arterial thrombosis (excluding stroke, subarachnoid haemorrhage, and myocardial infarction) was no longer statistically significant in the multivariate analysis, the risks associated with all the other past histories remained strong, with relative risks similar to those shown in table 4.

Discussion

This study provides estimates of the relative risk of stroke and myocardial infarction in women associated with various factors that are easily assessed in general practice in the United Kingdom. These risk estimates are quite precise, being based on 603 cases of stroke and myocardial infarction made available through the collaboration of a large number of group general practices over an extended period of time. Because this was a case-control study, it was not appropriate to measure a number of other risk factors, such as serum cholesterol, weight, and blood pressure, because they might have been changed by the acute stroke or myocardial infarction itself.

Since the interviews and the retrieval of information from the medical notes were performed by practice nurses who knew whether the woman was a case or control, some bias is possible. Because the main emphasis of the study was on the use of hormonal replacement therapy, however, it seems likely that the data reported in this paper would have been collected with the same thoroughness for controls as for cases. Where the abstraction of data from the medical notes was checked by an independent quality control nurse, there was no apparent tendency for the practice nurse to over-report positive medical histories in case patients. It is possible that the information on family history, which was obtained by interview, may have led to estimated relative risks slightly inflated by recall bias.

The present study suggests that single women have a lower risk of stroke and myocardial infarction than married women. These findings are supported by the Framingham Study which found that among clerical workers, single women had lower risks of coronary heart disease than married women who had raised children.[7] Other studies have suggested that women who are widowed, divorced, or separated are more likely to develop coronary heart disease,[8] but this was not seen in the present study.

Only a few studies found an association of parity with the risk of coronary heart disease in women. Where an association was found, multiparous women had a higher risk of coronary heart disease than nulliparous women,[9 10] but most studies did not find such an association.[11] In the present study, no association between parity and the risk of stroke and myocardial infarction was evident, especially after adjustment for marital state. Only 11% of the married women were nulliparous, so that marital state and parity were somewhat interrelated. The potential confounding effects of both age and marital state need to be carefully controlled in studies on parity.

Whereas it is generally found that current oral contraceptive use is associated with a threefold to fourfold increase in the risk of myocardial infarction and stroke,[12] the effects of oral contraceptives after their use has ceased are more uncertain. An increased risk of stroke, but not myocardial infarction, lasting more than six years after cessation of oral contraceptive use has been suggested.[13] In one case-control study of myocardial infarction, no association with past oral contraceptive use was found overall[14]; however, an increased risk was evident in those past users of oral contraceptives in whom the duration of use was greater than five years.[15] In the present study, we found no significant association of the past use of oral contraceptives with the risk of stroke and myocardial infarction; the low rate of past oral contraceptive use (9% of the women) precluded the useful subdivision of the data according to time since last use and type of cardiovascular event. Possibly, in a similar way, the low proportion of women who were premenopausal may have prevented the demonstration of a greater cardiovascular risk in postmenopausal than in premenopausal women of the same age, which has been found by others.[16 17]

In the present study, women who smoked cigarettes had about 2·5 times the risk of stroke and myocardial infarction compared with women who had never smoked. This is a consistent finding in studies of women[18] as well as in studies of men. In the Medical Research Council's Mild Hypertension Trial, women had greater relative risks associated with smoking than men, for both stroke and myocardial infarction.[19] The finding of a decreasing relative risk with increasing age is supported by other studies of women[20] as well as those of men. Overall, ex-smokers had only a marginally higher risk of stroke and myocardial infarction than women who had never smoked. Subdivision of the data according to time since giving up smoking, however, showed that those who had given up in the past five years still maintained a substantial proportion of the excess risk attributable to current smoking. No excess risk was evident in those women who had given up for ⩾10 years. Other studies of coronary heart disease showed similar results in men.[21] The mechanism by which smoking causes coronary heart disease thus has long term effects which are not rapidly reversible on giving up smoking.

Family history is an important risk factor for coronary heart disease; studies in general have shown about a twofold risk associated with a parental history of coronary heart disease.[22-24] Similar or more extreme results have been found for siblings. In the present study we did not know the age at which a parent or sibling developed a myocardial infarction or stroke, and the family history considered was that for any parent or sibling. There was a notable distinction between the relevance of family histories of myocardial infarction and that of stroke; while a family history of myocardial infarction was similarly related to the risk of both stroke and myocardial infarction in the index subject, a family history of stroke was not apparently related to either. This is despite the fact that hypertension, and to a lesser extent smoking habits, have tendencies to aggregate in families,[22] and that a family history of stroke has been found to be related to the risk of stroke in women in a previous study.[25]

The relations seen between past medical history and the risk of stroke and myocardial infarction (table 4) are mainly expected, at least in qualitative terms. Both hypertension and a past history of stroke or subarachnoid haemorrhage were more strongly related to the risk of stroke than to the risk of myocardial infarction. In contrast, past histories of diabetes and myocardial infarction were related similarly to the risk of myocardial infarction and of stroke. Diabetes is one of the risk factors for coronary heart disease that is more important in women than men, with the result that women with diabetes have a risk of myocardial infarction similar or only slightly lower than that of diabetic men.[26 27] So while diabetes is associated with about a twofold increase in coronary heart disease risk in men,[28] the relative risk for women in this study was tenfold. Although the past histories considered were somewhat interrelated, their independent associations with risk (as expressed in a multivariate analysis) remained important, and their importance was only slightly diminished as compared with when each past history was considered singly.

The slightly increased risk of myocardial infarction seen in this study associated with a past history of gynaecological cancers does not have an obvious explanation; allowance for smoking or other risk factors did not remove the apparent excess risk. It may be that the relation between haemostasis and malignancy[29] is also expressed in an increased risk of myocardial infarction in women with a past history of cancer.

The importance of a past history of venous thrombosis for the future risk of myocardial infarction found in the present study has not been described before. The most obvious common risk factors for venous and arterial events are haemostatic variables.[30 31] This finding supports the hypothesis that raised concentrations of certain coagulation factors or decreased fibrinolytic activity may predispose to thrombosis, there being evidence for this in both population studies[32] and clinical studies.[33–35]

We thank the doctors and nurses in the Medical Research Council's General Practice Research Framework who participated in this study and Professor Hugh Tunstall-Pedoe who undertook the substantial task of assessing the cases of stroke and myocardial infarction. We also thank Pat O'Kelly for the extra clerical and data-processing work in the study.

References

1. Office of Population Censuses and Surveys. *Mortality statistics by cause for England and Wales, 1985*. Series DH2 no 12. London: HMSO, 1987.
2. Thompson SG, Meade TW, Greenberg G. The use of hormonal replacement therapy and the risk of stroke and myocardial infarction in women. *J Epidemiol Community Health,* 1989;43 (in press)
3. Medical Research Council's Working Party on mild to moderate hypertension. Randomized controlled trial of treatment of mild hypertension: design and pilot trial *Br Med J* 1977;i.1437–40.
4. World Health Organization Regional Office for Europe. *Myocardial infarction community registers*. (Public Health in Europe No. 5). Copenhagen: World Health Organization, 1976.
5. Aho H, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community; results of a WHO collaborative study. *Bull WHO* 1980;58:113–30.
6. Breslow NE, Day NE. *Statistical methods in cancer research. Volume 1: The analysis of case-control studies.* Lyon: International Agency for Research on Cancer, 1980.
7. Haynes SG, Feinleib M. Women, work and coronary heart disease: prospective findings from the Framingham Heart Study. *Am J Public Health* 1980;70· 133–41.
8. Haynes SG. Type A behaviour, employment status, and coronary heart disease in women—a review. In: Oliver MF, Vedin A, Wilhelmsson C, eds. *Myocardial infarction in women*. Edinburgh: Churchill Livingstone, 1986:66–92.
9. Oliver MF. What is the difference between men and women? In: Oliver MF, Vedin A, Wilhelmsson C, eds. *Myocardial infarction in women*. Edinburgh: Churchill Livingstone, 1986:215–21.
10. Wilkelstein W Jr, Stenchever MA, Lilienfeld AM. Occurrence of pregnancy, abortion, and artificial menopause among women with coronary artery disease: a preliminary study. *J Chronic Dis* 1958;7: 273–86.
11. Bonnar J. Effects of physiological changes in sex hormones on potential coronary risk factors. In: Oliver MF, ed. *Coronary heart disease in young women*. Edinburgh: Churchill Livingstone, 1978: 107–17.
12. Stadel BV. Oral contraceptives and cardiovascular disease. *N Engl J Med* 1981,305.612–8 and 672–7.
13. Royal College of General Practitioners' Oral Contraception Study. Incidence of arterial disease amongst oral contraceptive users. *J R Coll Gen Pract* 1983; 33:75–82.
14. Slone D, Shapiro S, Kaufman DW, Rosenberg L, Miettinen OS, Stolley PD. Risk of myocardial infarction in relation to current and discontinued use of oral contraceptives. *N Engl J Med* 1981;305:420–4.
15. Shapiro S. Continued effects of oral contraceptives after cessation of treatment In: Oliver MF, Vedin A, Wilhelmsson C, eds. *Myocardial infarction in women.* Edinburgh: Churchill Livingstone, 1986·119–29.
16. Gordon T, Kannel WB, Hjortland MC, McNamara PM. Menopause and coronary heart disease. The Framingham Study. *Ann Intern Med* 1978;89: 157–61.
17. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. Menopause and the risk of coronary heart disease in women. *N Engl J Med* 1987;316:1105–10.
18. Doll R, Gray R, Haffner B, Peto R. Mortality in relation to smoking· 22 years' observations on female British doctors. *Br Med J* 1980;i:967–71.
19. Medical Research Council Working Party. Stroke and coronary heart disease in mild hypertension: risk factors and the benefit of treatment. *Br Med J* 1988; 296:1565–70.
20. Rosenberg L, Shapiro S, Kaufman DW, Slone D, Miettinen OS, Stolley PD. Cigarette smoking in relation to the risk of myocardial infarction in young women. Modifying influence of age and predisposing factors. *Int J Epidemiol* 1980;9:57–63.
21. Cook DG, Shaper AG, Pocock SJ, Kussick SJ. Giving up smoking and the risk of heart attacks. *Lancet* 1986; ii:1376–80.
22. Rissanen AM. Familial occurrence of coronary heart disease and major risk factors. In: Oliver MF, Vedin A, Wilhelmsson C, eds. *Myocardial infarction in women*. Edinburgh: Churchill Livingstone, 1986: 18–33.
23. Phillips AN, Shaper AG, Pocock SJ, Walker M. Parental death from heart disease and the risk of heart attack. *Eur Heart J* 1988;9:243–51.
24. Colditz GA, Stampfer MJ, Willet WC, Rosner B,

Speizer FE, Hennekens CH. A prospective study of parental history of myocardial infarction and coronary heart disease in women. *Am J Epidemiol* 1986;**123**: 48–58.

25 Khaw K, Barrett-Connor E. Family history of stroke as an independent predictor of ischaemic heart disease in men and stroke in women. *Am J Epidemiol* 1986;**123**: 59–66

26 Marks HH, Krall LP. Onset, course, prognosis and mortality in diabetes mellitus In: Marble A, White P, Bradley RF, Krall LP, eds. *Joslin's diabetes mellitus.* 11th ed. Philadelphia: Lea and Febiger, 1971:209–54.

27 Fuller JH, Head JA. Factors related to mortality in 5600 diabetic patients from 12 international centres [Abstract]. *Diabetologia* 1986;**29**:539a.

28 Shaper AG, Pocock SJ, Phillips AN, Walker M. Identifying men at high risk of heart attacks: strategy for use in general practice. *Br Med J* 1986;**293**:474–9.

29 Muszbek L, ed. *Haemostasis and cancer*. Florida: CRC Press, 1987.

30 Ducimetiere P, Richard JL, Pequignot G, Warnet JM. Varicose veins: a risk factor for atherosclerotic disease in middle-aged men? *Int J Epidemiol* 1981;**10**:329–35.

31 Meade TW, Brozovic M, Chakrabarti RR, *et al.* Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. *Lancet* 1986;ii:533–7.

32 Meade TW. Clotting factors and ischaemic heart disease: the epidemiological evidence. In: Meade TW, ed. *Anticoagulants and myocardial infarction: a reappraisal.* Chichester: Wiley, 1984.

33 Rocha E, Alfaro MJ, Paramo JA, Canadell JM. Preoperative identification of patients at high risk of deep venous thrombosis despite prophylaxis in total hip replacement. *Thromb Haemost* 1988;**59**:93–5.

34 Boyer C, Wolf M, Rothschild C, *et al.* An enzyme immunoassay (ELISA) for the quantitation of human factor VII. *Thromb Haemost* 1986;**56**:250–5

35 Davies JA. Detection of a pre-thrombotic state. In: Bloom AL, Thomas DP, eds. *Haemostasis and thrombosis.* 2nd ed. Edinburgh: Churchill Livingstone, 1987:721–38.

Br Heart J 1989;61:410–6

Prognostic significance of programmed ventricular stimulation in survivors of acute myocardial infarction

ANIL K BHANDARI, ROBERT HONG, ADAM KOTLEWSKI,
NANCY McINTOSH, PHILLIP AU, ANTHONY SANKOORIKAL,
SHAHBUDIN H RAHIMTOOLA

From the Section of Cardiology, Department of Medicine, LAC-USC Medical Center, University of Southern California School of Medicine, Los Angeles, California, USA

SUMMARY The prognostic significance of the response to programmed ventricular stimulation was studied in 75 stable survivors of acute myocardial infarction. Programmed ventricular stimulation induced sustained ventricular arrhythmias in 33 (44%) patients and did not induce these arrhythmias in 42 (56%) patients. During a mean follow up of 18 months, four patients died suddenly and three developed spontaneous sustained ventricular tachycardia. The occurrence of arrhythmic events was not significantly different in patients with inducible sustained arrhythmias and those without, but such events were predicted by the presence of mild congestive heart failure. Although the inducibility of sustained ventricular tachycardia (but not ventricular fibrillation) seemed to identify a high risk subset with an arrhythmic event rate of 21% compared with 5·5% in others, it had a low sensitivity (57%) and a low positive predictive accuracy (21%) for arrhythmic events.

Programmed ventricular stimulation is not helpful in identifying a subset of patients at high risk after an uncomplicated acute myocardial infarction.

In survivors of acute myocardial infarction mortality in the first year after discharge from hospital varies from 7 to 11%.[1-3] Sudden cardiac death accounts for about half of the deaths and is probably caused by ventricular tachycardia or fibrillation. In recent years several investigators have examined the value of programmed ventricular stimulation in identifying a subset at an increased risk of sudden death,[4-11] but the results have been conflicting. Moreover, none of the reported studies used a standard stimulation protocol of three extrastimuli or compared the prognostic significance of inducible ventricular arrhythmias with that of other prognostic variables.

We assessed the prognostic value of the induced response to programmed ventricular stimulation in a prospective study of clinically stable survivors of acute myocardial infarction. We also used a stepwise Cox regression analysis to assess the value of programmed ventricular stimulation against other known clinical, electrocardiographic, and angiographic prognostic variables.

Patients and methods

Patients aged ≤70 years admitted to the intensive cardiac care unit of our hospital with a diagnosis of an acute myocardial infarction were screened for the study. Myocardial infarction was diagnosed according to clinical, electrocardiographic, and enzymatic criteria. Patients were eligible if they were clinically stable and did not have Killip class III or IV congestive heart failure, moderate to severe angina pectoris, or spontaneous sustained ventricular tachycardia in the 48 hours after myocardial infarction. Patients were excluded if they had end stage disease of another organ system or if they refused to participate in the study.

From September 1983 to June 1985, 164 patients with a confirmed diagnosis of acute myocardial infarction were eligible for the study. There were 17

Requests for reprints to Dr Anil K Bhandari, USC School of Medicine, Section of Cardiology, 2025 Zonal Avenue, Los Angeles, CA 90033, USA.

Accepted for publication 20 December 1988

deaths in hospital. Seventy two patients were excluded by predetermined criteria (table 1). We studied the remaining 75 (51%) consenting patients (mean age 53 (9) years (range 35 to 67 years)), including the 45 patients whose initial preliminary findings have been previously reported.[10]

The infarct was anterior in 36 patients (48%) and inferior in 39 patients (52%). Fourteen patients had mild congestive heart failure and 16 had mild angina pectoris. The mean peak creatine kinase activity was 1928 (1607) IU/l (range 250–7250 IU/l) with an MB isoenzyme fraction of 16 (9)% (7–35%). The medications at the time of the study included digoxin in nine patients, diuretics in 14 patients, nitrates in 56 patients, and calcium channel antagonists in 12 patients.

METHODS

After giving their written informed consent patients had 24 hour ambulatory electrocardiographic monitoring, programmed ventricular stimulation, and cardiac catheterisation with coronary angiography. These tests were performed within 7–18 (11 (3)) days after the infarct. Programmed ventricular stimulation and cardiac catheterisation were performed together on the same day after an average of 14 (5) days (9–21 days) after the infarct.

Programmed ventricular stimulation was performed with patients in the postabsorptive and unsedated state. Surface electrocardiographic leads (V1, I, and aVF) and intracardiac electrograms were displayed and recorded on an oscilloscopic photographic recorder (Electronics for Medicine, VR-16) at a paper speed of 25 mm/s. Stimuli of 2 ms at twice the diastolic threshold (minimum pacing current, 1·5 mA) were provided by a digital programmable stimulator (Bloom and Associates). The stimulation protocol was uniform in each patient and has been described in detail previously.[10] Briefly, the stimulation was always started at the right ventricular apex with burst pacing (500–280 ms) followed by a sequential insertion of single and double extrastimuli at paced cycle lengths of 500 and 400 ms. If sustained ventricular tachycardia or fibrillation was not induced, the same steps were repeated at the right ventricular outflow tract and then at the left ventricular apex. Triple extrastimuli were used only after double extrastimuli at all three sites had failed to induce sustained arrhythmias.

Table 1 *Selection of patients for participation in the study*

Selection process	*Patients (n)*	
Patients admitted with acute Q wave MI	164	
Deaths in hospital	17	
Patients screened for study	147	
Exclusions from study	72	(49%)
Moderate to severe angina	12	
Killip class III or IV CHF	16	
Sustained VT	3	
End stage disease	11	
Patient refusal	30	
Patients participating in study	75	(51%)

MI, myocardial infarction, CHF, congestive heart failure; VT, ventricular tachycardia.

Sustained ventricular tachycardia was defined as that which lasted 30 seconds or longer or caused haemodynamic compromise and had to be terminated in less than 30 seconds by direct current counter shock or overdrive pacing. Non-sustained ventricular tachycardia was defined as that which lasted from six beats to less than 30 seconds and did not cause haemodynamic compromise. Ventricular fibrillation was defined as a disorganised rapid ventricular activity requiring immediate defibrillation because of haemodynamic compromise.

Cardiac catheterisation with angiography was performed 15–30 minutes after completion of programmed ventricular stimulation. The criterion for a significant coronary artery stenosis was a reduction of ⩾70% in the internal diameter of the vessel. Left ventricular angiograms were performed in the 30° right anterior oblique (75 patients) and in the 55° left anterior oblique projections (73 patients). A quantitative score of the left ventricular wall motion abnormality was determined in both the right anterior oblique and left anterior oblique projections by a previously described method.[12] Each projection was divided into five segments and the contraction of each segment was scored as follows: normal = 1, moderate hypokinesia = 2, severe hypokinesia = 3, akinesia = 4, and dyskinesia = 5. A quantitative score was obtained by adding the assigned value to each segment of the ventricle. With this system, a score of 10 equals normal wall motion function, 10–15 indicates a slight abnormality, 15–25 a moderate abnormality, and >25 a severe wall motion abnormality of the left ventricle.

FOLLOW UP AND STATISTICAL ANALYSIS

Fifty two of the 75 patients were followed in the cardiology clinics of the Los Angeles County–University of Southern California Medical Center at regular intervals of 4–16 weeks. In others the follow up data were obtained by telephone either from the patient or from the patient's private physician. The study end points were death or the development of documented spontaneous sustained ventricular tachycardia or fibrillation. Sudden death was defined as death within an hour of the onset of terminal symptoms or that which occurred unexpectedly without any premonitory symptoms.

Values were expressed as mean (SD). Statistical analysis was performed by a χ^2 test or t test as appropriate. The actuarial probability curves were constructed according to the method of Kaplan and Meier.[13] First, the univariate predictors of arrhythmic events were determined by a χ^2 test. Then we used stepwise Cox regression analysis to determine variables of independent prognostic significance. The variables in this analysis included the following: presence or absence of congestive heart failure; site of acute myocardial infarction; left ventricular ejection fraction; left ventricular wall motion abnormality score; and inducibility of sustained ventricular tachycardia, ventricular fibrillation, or both.

Results

RESPONSE TO PROGRAMMED VENTRICULAR STIMULATION

Programmed ventricular stimulation induced sustained ventricular tachycardia in 19 patients and ventricular fibrillation in 14 patients. These 33 patients were assigned to group 1. These arrhythmias were induced by right ventricular stimulation in 24 patients and left ventricular stimulation in nine patients. The cycle length of ventricular tachycardia ranged from 200 to 290 ms (mean 232 (16) ms); the QRS complexes were of right bundle branch block configuration in 11 patients and of left bundle branch block configuration in eight patients. Sustained ventricular tachycardia was induced by two extrastimuli in 11 patients, three extrastimuli in seven patients, and burst pacing in one patient. Induction of ventricular fibrillation required two extrastimuli in six patients and three extrastimuli in eight patients.

Programmed ventricular stimulation did not induce sustained ventricular arrhythmias in 42 patients (group 2). In six of them non-sustained ventricular tachycardia was induced (uniform in four patients and multiform in two). Induction required two extrastimuli in two patients and triple extrastimuli in four patients.

Table 2 summarises the clinical, haemodynamic, and angiographic characteristics of patients in each group. Group 1 patients had an increased frequency of mild congestive heart failure, and a higher value for peak serum creatine kinase, pulmonary artery wedge pressure, and left ventricular wall motion abnormality score. However, the two groups did not significantly differ for 24 hour ambulatory electrocardiographic monitoring or treadmill testing, location of the infarct, left ventricular angiographic ejection fraction, and the frequency of left ventricular aneurysms.

Table 2 *Profile of patients with inducible sustained ventricular tachycardia or fibrillation and without*

	Sustained VT/VF		
Variable	*Inducible (n = 33) (group 1)*	*Non-inducible (n = 42) (group 2)*	*p value*
Peak creatine kinase (IU/l)*	2347 (1739)	1592 (1426)	<0·005
Mild CHF (Killip class II)	10 (33%)	4 (10%)	<0·01
Anterior MI	15 (45%)	21 (50%)	NS
PVCs/h*	326 (1267)	282 (631)	NS
PAW (mm Hg)*	16·4 (7·6)	13·3 (5·8)	<0·05
LV angiographic WMA score*	22 (6)	19 (6)	<0·05
LV ejection fraction*	0·47 (0·15)	0·48 (0·11)	NS
LV aneurysm	12 (36%)	11 (26%)	NS
No of diseased coronary arteries*	2·2 (0·4)	2·1 (0·3)	NS

*Mean (SD).
CHF, congestive heart failure; MI, myocardial infarction; PVCs, premature ventricular contractions; LV, left ventricular; PAW, pulmonary artery wedge pressure; WMA, wall motion abnormality

FOLLOW UP OBSERVATIONS AND TREATMENT

The follow up ranged from four to 36 (18 (7)) months and was complete in all but five patients (two in group 1 and three in group 2) who moved out of the country 4–8 months after the index infarction. β Adrenergic blockers were given to only seven patients (four in group 1 and three in group 2) for control of angina, hypertension, or both. Prophylactic antiarrhythmic treatment was not routinely administered except for the first 10 patients in group 1 who received procainamide or quinidine for the first 3–6 months. Six patients in group 1 and five in group 2 underwent coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, or both for left main coronary disease or for symptoms of intractable angina.

At the end of an average 18 months follow up, arrhythmic events had occurred in seven patients: these were sudden death in four patients and non-fatal spontaneous sustained ventricular tachycardia in three patients. None of the seven patients was on antiarrhythmic treatment at the time of the arrhythmic events, although two patients had received this treatment in the preceding year. One group 1 patient died of progressive heart failure 11 months after the infarction. Thus the overall total cardiac mortality was 6·7% (five of 75 patients) and the mortality caused by sudden death was 5·3%. In addition, non-fatal recurrent myocardial infarction developed in three group 1 patients and in one group 2 patient.

INDUCIBILITY IN RELATION TO ARRHYTHMIC EVENTS

There were arrhythmic events in five (15%) of 33 patients in group 1 compared with two (5%) of 44 patients in group 2 ($p < 0{\cdot}4$). The two year probability of remaining free of arrhythmic events was 0·83 for patients in group 1 and 0·95 in group 2 (p < 0·4) (fig 1a). Among group 1 patients, three patients died suddenly 15, 16, and 26 months after the index infarct and two patients had spontaneous sustained ventricular tachycardia at two weeks and 26 months after the infarct. Three extrastimuli were required to induce sustained arrhythmias in two of these five patients. Arrhythmic events did not develop in any of the nine patients in whom induction of sustained arrhythmias had required left ventricular stimulation. One patient in group 2 died suddenly three months after the index infarct and one had spontaneous sustained ventricular tachycardia two months after the infarct. The maximum induced response in both patients was less than three repetitive ventricular beats.

The risk of arrhythmic events was highest in a subset of 19 group 1 patients in whom sustained ventricular tachycardia was induced. Arrhythmic events occurred in four (three sudden deaths and one sustained ventricular tachycardia) of these 19 patients compared with three of the remaining 56 patients in whom arrhythmia was not inducible or in whom only ventricular fibrillation was induced. The two year probability of remaining free of arrhythmic events was 0·73 and 0·95 respectively (p <0·06) (fig 1b). We then compared the tachycardia characteristics and other clinical and angiographic features of these four patients who had arrhythmic events with those in the remaining 15 patients with inducible sustained ventricular tachycardia but no arrhythmic events (table 3). The mean cycle length of the tachycardia was significantly higher in patients with arrhythmic events than in those without (252 (24) ms *v* 225 (21) ms, p < 0·05). Patients with arrhythmic events were more likely to have ventricular tachycardia induced by two extrastimuli, an increased number of diseased coronary arteries, and more repetitive ventricular extrasystoles and mild congestive heart failure.

For predicting subsequent arrhythmic events the inducibility of sustained ventricular arrhythmias had a sensitivity of 71%, a specificity of 60%, and a positive predictive accuracy of 15%. When sustained ventricular tachycardia (and not ventricular fibrillation) was considered to be the only criterion for a positive response, the corresponding values were 57%, 78%, and 21%.

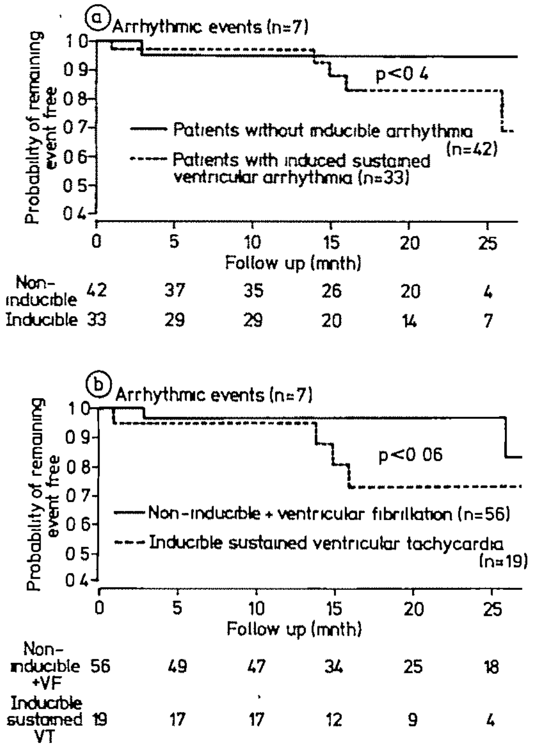


Fig 1 *Prediction of sudden death and non-fatal spontaneous sustained ventricular tachycardia by programmed ventricular stimulation.*

Table 3 *Clinical, angiographic, and electrophysiological characteristics of patients with inducible sustained ventricular tachycardia who had or did not have arrhythmic events*

Variable	*Patients with arrhythmic events (n = 4)*	*Patients without arrhythmic events (n = 15)*	*p value*
Anterior MI (n (%))	2 (50)	5 (33)	NS
Mild CHF (n (%)) (mean (SD))	3 (75)	7 (47)	NS
Peak creatine kinase (IU/l)	3137 (1245)	2019 (1403)	NS
PVC > 10/h* (n (%))	2 (50)	2 (13)	NS
Repetitive PVCs (n (%))	3 (75)	3 (20)	<0·07
LV ejection fraction:			
Mean (SD)	0·38 (0·9)	0·42 (0·17)	NS
<0·45 (n (%))	3 (75)	8 (53)	NS
LVEDP (mm Hg) (mean (SD))	20 (8)	23 (8)	NS
LV WMA score (mean (SD))	25 (2)	25 (5)	NS
No coronary arteries diseased (mean (SD))	2·7 (0·5)	1·9 (0·8)	0·09
LV aneurysm (n (%))	2 (50)	6 (40)	NS
VT cycle length:			
Mean (SD) (ms)	252 (24)	225 (21)	<0·05
>250 ms (n (%))	3 (75)	3 (20)	0·07
VT induction.			
No of extrastimuli (mean (SD))	2·25 (0·5)	2·73 (0·7)	NS
By ≤2 extrastimuli (n (%))	3 (75)	6 (40)	NS

*Mean hourly frequency during 24 hour ambulatory electrocardiographic recording. EDP, end diastolic pressure. See footnote to table 2 for other abbreviations.

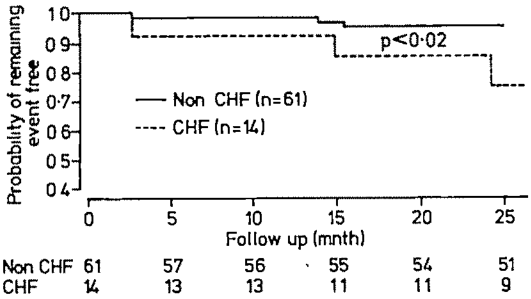


Fig 2 *Prediction of sudden death and non-fatal spontaneous sustained ventricular tachycardia by the presence or absence of mild congestive heart failure (CHF).*

ARRHYTHMIC EVENTS IN RELATION TO OTHER ARIABLES

A stepwise Cox regression analysis showed that mild congestive heart failure was the only significant predictor ($p < 0{\cdot}01$) of the subsequent arrhythmic events. There were arrhythmic events in four (29%) of the 14 patients with mild congestive heart failure and three (5%) of the remaining 61 patients. The two year probability of remaining free of arrhythmic events was 0·76 in patients with and 0·94 in those without heart failure ($p < 0{\cdot}02$) (fig 2). In the prediction of future arrhythmic events the presence of mild congestive heart failure had a sensitivity, specificity, and positive predictive accuracy of 57%, 85%, and 28% respectively.

Among group 1 patients there was no significant difference in the occurrence of arrhythmic events in patients who had received previous antiarrhythmic treatment and those who had not (20% *v* 13%, p = NS). None of the 11 patients (six group 1 and five group 2) who had procedures for coronary reperfusion developed arrhythmic events during follow up.

Discussion

This prospective study was designed to determine the prognostic significance of programmed ventricular stimulation in clinically stable survivors of an acute myocardial infarction. The overall total cardiac mortality was low (6·7%) after an average follow up of 18 months, and undoubtedly reflects the exclusion of high risk patients. In this low risk group, programmed ventricular stimulation performed two weeks after infarction induced sustained ventricular tachycardia or fibrillation in 44% of the patients. The incidence of inducibility was higher than that (20 to 33%) reported elsewhere[5-10 12] and was probably related to the vigor of the stimulation protocol in our study. We used a maximum of three extrastimuli delivered at both right and left ventricles. In contrast, in most of the earlier studies a maximum of two extrastimuli was used and left ventricular stimulation was not performed. The inducibility of sustained ventricular arrhythmias correlated with the indices of a larger infarct size, such as peak creatine kinase activities, the presence of congestive heart failure, and the left ventricular angiographic wall motion abnormalities. These findings accord with those previously reported in survivors of acute myocardial infarction.[5-12]

The inducibility of sustained ventricular arrhythmias did not predict future arrhythmic events. These events occurred in 15% of patients with inducible sustained arrhythimias and 5% of those without ($p = 0{\cdot}4$). The prognosis was best related to the presence or absence of mild congestive heart failure (29% *v* 5%, $p < 0{\cdot}02$). These findings accord with those of three previous studies that evaluated the prognostic significance of programmed ventricular stimulation in clinically stable survivors of acute myocardial infarction.[7-9] In these studies, however, the stimulation protocol included a maximum of two extrastimuli at twice diastolic threshold; conceivably, the lack of programmed ventricular stimulation may have lacked predictive value because the stimulation protocol was inadequate. Indeed, in our study, two of the five group 1 patients in whom arrhythmic events developed had required triple extrastimuli for induction of sustained arrhythmia, but triple extrastimuli also resulted in a much higher incidence (44%) of inducibility. Arrhythmic events did not develop in any of the nine group 1 patients who had required left ventricular stimulation for induction of sustained ventricular tachycardia or ventricular fibrillation.

Our findings differ from those of Denniss *et al* who performed programmed ventricular stimulation in 403 clinically stable patients with acute myocardial infarction.[11] They induced ventricular tachycardia (of longer than 10 seconds) or ventricular fibrillation in 34% of the patients and found that the two year probability of remaining free of arrhythmic events was significantly lower in patients with inducible ventricular tachycardia or ventricular fibrillation than in those without (0·84 *v* 0·95, $p < 0{\cdot}01$). In the two studies, however, patient characteristics and protocols for programmed ventricular stimulation differed. In our study, 51% of the surviving patients after infarction entered the study, whereas the study by Denniss *et al* included 81% of all survivors of acute myocardial infarction. Their study undoubtedly included more of the high risk patients. Cardiac death or non-fatal sustained ventricular arrhythmias developed in 9% of their patients during a follow up of 12 months compared with 7·3% of our patients after an average follow up of 18 months. In addition, Denniss *et al* used a non-standard protocol for programmed ventricular stimulation that included delivery of two extrastimuli at a high current strength of 20 mA. The available data on the specificity and sensitivity of this protocol are limited and controversial.[14 15] In contrast, the value of the protocol used in our study is well established for several clinical conditions, including patients with recurrent sustained ventricular tachycardia or cardiac arrest.[16-18]

The configuration of the induced arrhythmia seemed to be of prognostic significance. Four of the 19 patients with inducible uniform sustained ventricular tachycardia had an arrhythmic event during follow-up compared with three of the remaining 56 patients (21% *v* 5%, $p < 0{\cdot}06$). In contrast, induction of ventricular fibrillation seemed to be a non-specific response as only one of the 14 patients with this response had an arrhythmic event during follow up. Similar observations have recently been reported by Denniss *et al* who did not find an increased risk of arrhythmic events in patients with inducible ventricular fibrillation compared with those with no inducible arrhythmia (8% *v* 7%, p = NS).[11] In contrast, inducible ventricular tachycardia identified a subset (20% of all patients) that had a 27% probability of developing arrhythmic events within two years of infarction. In both studies, the patients with inducible ventricular tachycardia who developed arrhythmic events tended to have a longer cycle length for the induced ventricular tachycardia and a lower left ventricular ejection fraction. These findings were not unexpected and accord with the experimental observations in a canine model of myocardial infarction.[19] During serial programmed ventricular stimulation in 20 anaesthetised dogs, Garan *et al* showed a high week to week reproducibility (>90%) of inducible sustained uniform ventricular tachycardia, whereas induction of ventricular fibrillation was found to be a non-specific response.[19] These findings also accord with observations in human beings where day to day reproducibility has been shown to be high for sustained ventricular tachycardia and low for ventricular fibrillation induced in the post-infarction period.[20]

CLINICAL IMPLICATIONS

To be useful for identifying patients at risk of arrhythmic events, a test should have a high sensitivity and positive predictive accuracy and should also provide prognostic information independent of a routine clinical evaluation. In the present study, inducible sustained ventricular tachycardia had a low sensitivity (57%) and positive predictive accuracy (21%) for future arrhythmic events. Instead, outcome was best predicted by the presence or absence of mild congestive heart failure. Had we excluded the 14 patients with mild congestive heart failure from our study, programmed ventricular stimulation in the remaining 61 patients would have identified only one patient in whom an arrhythmic event developed. In previous prospective studies of programmed ventricular stimulation, the positive predictive accuracy of programmed ventricular stimulation was 18% and 32%,[5 11] and no study so far has shown the inducible arrhythmia to be an independent predictor of arrhythmic events. Moreover, programmed ventricular stimulation is an invasive and expensive test associated with a small but definite morbidity which can be performed at only a few laboratories with a highly trained staff. For these reasons, we believe that the routine use of this procedure is not recommended in clinically stable patients surviving an acute myocardial infarction. However, programmed ventricular stimulation may be of more value in patients whose post-infarction course is complicated by heart failure, angina pectoris, or ventricular tachycardia. A prospective study in such a high risk subset is already in progress at our medical centre. Among the first 53 patients studied, major arrhythmic events occurred in five of 10 patients with inducible sustained ventricular tachycardia and two of 43 (4·8%) patients in whom ventricular arrhythmias were non-inducible or who had induction of ventricular fibrillation ($p < 0{\cdot}01$).[21] These preliminary findings, though encouraging, need to be confirmed in a larger cohort of patients.

CRITIQUE OF THE STUDY

In this study, 10 of the 33 patients with inducible sustained arrhythmias received empirical antiarrhythmic treatment for the first 3–6 months, and this might have influenced outcome. However, no previous study has shown a beneficial effect of prophylactic antiarrhythmic treatment on survival in such patients. Moreover, antiarrhythmic treatment was not based on the results of electropharmacological testing, and two of these 10 patients had an arrhythmic event during follow up. β Adrenergic blocking agents were administered to only seven patients for control of angina or systemic hypertension. The outcome of the study population might also have been altered by the coronary artery bypass surgery, percutaneous transluminal coronary angioplasty, or both, which were performed in 11 patients (15%). Although none of these 11 patients had an arrhythmic event during follow up, the number of patients undergoing coronary reperfusion was too small to draw a meaningful conclusion. Also, there was no significant difference in the proportion of patients undergoing myocardial revascularisation between the two groups.

Supported by a grant from the GCRC Program of the Division of Research Resources, National Institute of Health.

References

1 The Multicenter Post-Infarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med* 1983;**309**·331–6.

2 Mukharji J, Rude RE, Poole KW, and the MILIS Study Group. Risk factors for sudden death after acute myocardial infarction: two year follow-up *Am J Cardiol* 1984;**54**:31–6.

3 Roubin GS, Harris PJ, Bernstein L, Kelly DT Coronary anatomy and prognosis after myocardial infarction in patients 60 years of age and younger *Circulation* 1983;**67**·743–9.

4 Hamer A, Vohra J, Hunt D, Sloman G. Prediction of sudden death by electrophysiologic studies in high risk patients surviving acute myocardial infarction. *Am J Cardiol* 1982;**50**:223–9

5 Waspe LE, Seinfeld D, Ferrick A, Kim SG, Matos JA, Fisher JD. Prediction of sudden death and spontaneous ventricular tachycardia in survivors of complicated myocardial infarction: value of the response to programmed stimulation using a maximum of three ventricular extrastimuli. *J Am Coll Cardiol* 1985;**5**: 1292–301.

6 Roy D, Marchand E, Theroux P, Waters D, Pelletier G, Bourassa M Programmed ventricular stimulation in survivors of an acute myocardial infarction. *Circulation* 1985;**72**:487–94.

7 Breithardt G, Borggrefe M, Haerten K. Role of programmed ventricular stimulation and noninvasive recording of ventricular late potentials for the identification of patients at risk of ventricular tachyarrhythmias after acute myocardial infarction. In: Zipes DP, Jalife J, eds *Cardiac electrophysiology and arrhythmias*. New York: Grune and Stratton, 1985: 553–61.

8 Marchlinski FE, Buxton AE, Waxman HL, Josephson ME. Identifying patients at risk of sudden death after myocardial infarction. value of the response to programmed stimulation, degree of ventricular ectopic activity and severity of left ventricular dysfunction..*Am J Cardiol* 1983;**52**:1190–6

9 Santarelli P, Bellocci F, Loperfido F, *et al.* Ventricular arrhythmia induced by programmed ventricular stimulation after acute myocardial infarction. *Am J Cardiol* 1985;**55**:391–4.

10 Bhandari AK, Rose JS, Kotlewski A, Rahimtoola SH, Wu D. Frequency and significance of induced sustained ventricular tachycardia or fibrillation two weeks after acute myocardial infarction. *Am J Cardiol* 1985;**56**:737–42.

11 Denniss AR, Richards DA, Cody DV, *et al.* Prognostic significance of ventricular tachycardia and fibrillation induced at programmed stimulation and delayed potentials detected on the signal-averaged electrocardiograms of survivors of acute myocardial infarction. *Circulation* 1986;**74**:731–45.

12 CASS Investigators. National Heart, Lung and Blood Institute Coronary Artery Surgery Study: Appendix C—Left ventriculography. *Circulation* 1981;**63** (suppl I):164–5.

13 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1985;**53**: 457–81.

14 Richards DA, Cody DV, Denniss AR, Russell PA, Young AA, Uther JB A new protocol of programmed stimulation for assessment of predisposition to spontaneous ventricular arrhythmias. *Eur Heart J* 1983; 4.376–82.

15 Brugada P, Wellens HJJ. Comparison in the same patient of two programmed ventricular stimulation protocols to induce ventricular tachycardia. *Am J Cardiol* 1985;**55**:380–3.

16 Brugada P, Green M, Abdollah H, Wellens HJJ. Significance of ventricular arrhythmias initiated by programmed ventricular stimulation: the importance of the type of ventricular arrhythmias induced and the number of premature stimuli required. *Circulation* 1984;**69**:87–92.

17 Kudenchuck PJ, Kron J, Walance CG, *et al.* Reproducibility of arrhythmia induction with intracardiac electrophysiologic testing: patients with clinical sustained ventricular tachyarrhythmias. *J Am Coll Cardiol* 1986;**7**:819–28.

18 Mason J, Winkle R Electrode-catheter arrhythmia induction in the selection and assessment of antiarrhythmic drug therapy in recurrent ventricular tachycardia. *Circulation* 1978;**58**:971–85.

19 Garan H, Ruskin J, McGovern B, Grant B. Serial analysis of electrically induced ventricular arrhythmias in a canine model of myocardial infarction. *J Am Coll Cardiol* 1985;**5**:1095–106.

20 Hong R, Bhandari A, Kulick D, Rubin JN, McIntosh N, Rahimtoola SH Day-to-day reproducibility of response to programmed ventricular stimulation in patients with recent acute myocardial infarction [Abstract] *J Am Coll Cardiol* 1988;**11**:5A.

21 Bhandari A, Hong R, Kotlewski A, Rubin JN, McIntosh N, Rahimtoola SH. Prognostic significance of programmed stimulation in high risk patients surviving acute myocardial infarction [Abstract] *J Am Coll Cardiol* 1988;**11**:6A.

Br Heart J 1989;61:417–20

Percutaneous transluminal angioplasty of left internal mammary artery grafts: two years' experience with a femoral approach

MALCOLM R BELL, DAVID R HOLMES JR, RONALD E VLIETSTRA, DENNIS R BRESNAHAN

From the Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA

SUMMARY Percutaneous transluminal angioplasty via the femoral approach was attempted through internal mammary artery grafts in 11 patients who presented with distal anastomotic stenoses or distal native coronary artery stenoses and angina pectoris. The procedure was technically successful in 10 patients and no major complications occurred. During follow up there was one late death, but all 10 surviving patients showed functional improvement.

Percutaneous transluminal angioplasty seems to be a safe and effective treatment for stenoses of internal mammary artery grafts. This is an effective technique for treating the increasing number of patients who are likely to present with stenoses of these grafts.

The success of percutaneous transluminal angioplasty of saphenous vein grafts[1] has prompted its use in stenoses of internal mammary artery grafts, and the results in a small number of selected patients have been very encouraging.[2-4] None the less, concern has been expressed about the technical difficulties and the risks of the femoral artery approach when angioplasty of these grafts is attempted.[2 5]

We report our experience and follow up results with percutaneous transluminal angioplasty of internal mammary artery grafts from the femoral approach.

Patients and methods

DATA ACQUISITION

We reviewed all cases of percutaneous transluminal angioplasty of internal mammary artery grafts performed at the Mayo Clinic up to and including July 1988. Clinical and follow up data were obtained from the medical history, from our angioplasty registry, and by interviewing the patient. Cineangiographic films of all patients were reviewed.

TECHNIQUE AND EQUIPMENT

Our approach to dilating internal mammary artery grafts was through the femoral artery. Arterial access was established with an 8 F sheath. A Judkins size 4 right coronary diagnostic catheter was advanced to the aortic arch and into the left subclavian artery. A 0·035 inch (0·89 mm) flexible J tip "long exchange" wire was then advanced to the axillary artery and the diagnostic catheter was exchanged for an 8 F internal mammary artery guiding catheter (USCI Division, C R Bard, Inc, Billerica, Massachusetts). This catheter was then slowly withdrawn, with the tip directed anteriorly and inferiorly, until it engaged the ostium of the internal mammary artery. Although pressure damping was noted occasionally after engagement of the ostium, this did not result in clinical problems.

We recommend a low profile trackable balloon to negotiate the sometimes tortuous internal mammary artery (table 1). We had no difficulty in stabilising the guiding catheter while attempting to cross any stenosis.

We used a non-ionic contrast medium to help minimise any chest wall, neck, or arm discomfort associated with contrast injection and to reduce the

Requests for reprints to Dr David R Holmes Jr, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905, USA

Accepted for publication 6 January 1989

Table 1 *Specifications of balloon dilatation catheters used for angioplasty of internal mammary artery grafts*

Balloon catheter	*Frequency of use (no of patients)*
Hartzler LPS, 20 mm (2 to 3 mm)*	9
Probe Balloon (2 5 mm)†	2
Profile Plus 20–25†	1

*Advanced Cardiovascular Systems, Inc, Temecula, California.
†USCI Division, C R Bard Inc, Billerica, Massachusetts.

risk of neurotoxicity should the vertebral artery be injected.

Results

PATIENTS

We report on 11 patients (six men and five women, mean (SD) age 58 (11) years) (table 2). The median interval between graft implantation and subsequent angioplasty was six months (range five days to six years). All 11 patients had angioplasty involving the left internal mammary artery graft, which was implanted into the left anterior descending artery in 10 patients and into an obtuse marginal artery in one. The stenoses affected a distal anastomotic site (seven cases) and the native coronary artery distal to the anastomosis (four cases) (figs 1 and 2). In the latter four patients the mammary artery was used as a conduit to reach the distal vessel.

OUTCOME AND COMPLICATIONS OF ANGIOPLASTY

Dilatation was regarded as successful (that is, there was at least a 40% reduction in the visually assessed lumen diameter narrowing) in 10 patients (91%). The mean (SD) reduction in luminal diameter of 93 (5)% before dilatation was reduced to 30 (24)% after dilatation. The only failure occurred in a patient (case 4) with a 90% stenosis of the distal left anterior descending artery. The stenosis was successfully crossed with a balloon but could not be dilated. One patient (case 1) had transient occlusion at the site of angioplasty during dilatation of the distal mammary anastomosis; this was successfully recrossed and dilated with no clinical sequelae. There were no other complications in this series.

FOLLOW UP

We followed all 11 patients (mean (SD) 12 (7) months; range 2–22 months). There was an improvement in functional class in 10 patients, four of whom remained symptom free (fig 3). A 76 year old woman (case 8) who had successful dilatation of an internal mammary artery graft after resuscitation from an out of hospital cardiac arrest died at home (unwitnessed) two months later. There were no myocardial infarctions during follow up in any patient.

Two patients (cases 5 and 7) had repeat coronary angiography (one month after angioplasty), and patency of the internal mammary artery grafts was shown in each case. One patient (case 5) required a repeat coronary operation because of incomplete revascularisation.

Discussion

The superior patency rates and improved survival of patients when the internal mammary artery is used as a coronary bypass conduit compared with the saphenous vein have been established[6]; as a consequence, use of the internal mammary artery is increasing rapidly.[7] Angiographic and postmortem studies have shown a very low frequency of atherosclerosis in this artery.[8-10] Although the internal mammary artery is a better conduit, it can become stenosed at the distal anastomotic site.[11] Furthermore, disease in the native vessel distal to the graft insertion may progress. As the number of patients with internal mammary artery grafts increases, we

Table 2 *Clinical and technical data from 11 patients with stenosis of internal mammary artery grafts*

Case	*Age (yr)*	*Interval between grafting to PTA*	*Site*	*Stenosis (%)*		*Complications*
				Pre-PTA	*Post-PTA*	
1	66	3 mnth	DA	80	30	IMA graft and LAD occlusion (redilated)
2	44	13 mnth	NDV	95	30	None
3	61	5 mnth	DA	95	20	None
4	68	2 mnth	NDV	90	90	None
5	46	14 mnth	DA	90	10	None
6	58	50 mnth	NDV	99	30	None
7	65	2 mnth	DA	95	20	None
8	76	11 mnth	DA	90	30	None
9	43	5 day	DA	95	50	None
10	55	74 mnth	DA	100	0	None
11	63	6 mnth	NDV	90	20	None

DA, distal anastomosis; IMA, internal mammary artery, LAD, left anterior descending artery, NDV, native distal vessel, PTA, percutaneous transluminal angioplasty

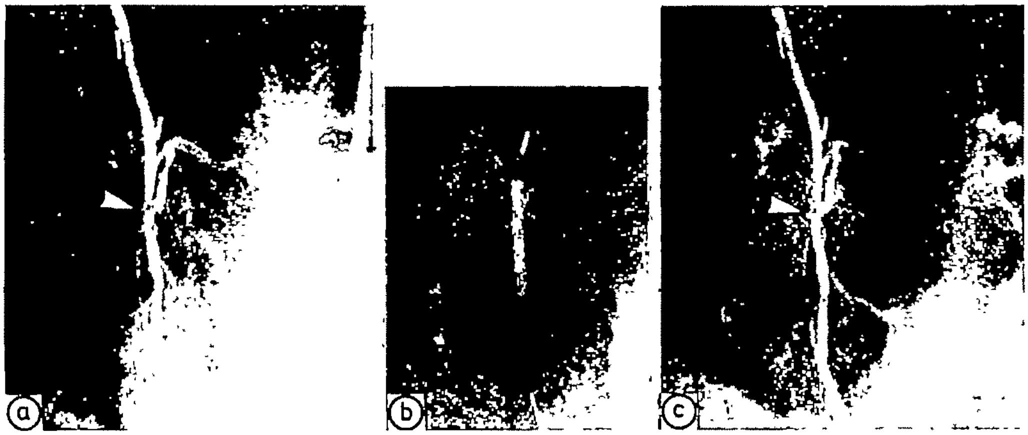


Fig 1 *Angiograms during angioplasty of internal mammary artery graft at distal anastomotic site (a) A 90% stenosis (arrowhead) at anastomosis of graft and left anterior descending artery. (b) Angioplasty balloon inflated within lesion. (c) Subsequent angiogram shows minimal residual stenosis (arrowhead).*

can expect a growing number of patients with postoperative stenosis of the graft or distal vessel.

We have shown in a small number of patients that angioplasty of left internal mammary artery grafts can be safely and successfully performed from the femoral approach. Early follow up showed significant improvement in anginal symptoms in most patients, and none required repeat dilatation for restenosis.

Some favour the ipsilateral brachial artery approach for angioplasty of internal mammary artery graft stenoses to overcome the potential problems with cannulating and then maintaining stability of the guiding catheter positioned from the femoral artery.[2 5] In a recent series, however, use of this approach was not without complication: three of eight procedures were complicated by ventricular fibrillation, internal mammary artery spasm, or dissection.[2]

Pinkerton *et al* recently described their success with angioplasty of internal mammary artery grafts

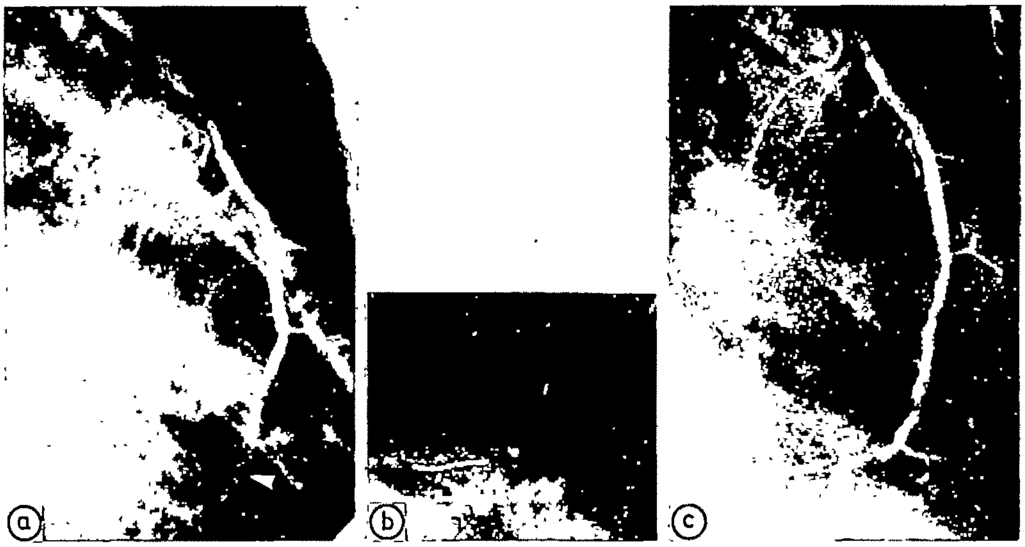


Fig 2 *Angiograms from patient with acute inferior myocardial infarction. (a) Angioplasty performed via internal mammary artery graft to dilate occluded distal left anterior descending artery (arrowhead). (b) Balloon inflated at site of occlusion. (c) Subsequent angiogram showing successful dilatation with filling of distal left anterior descending artery*

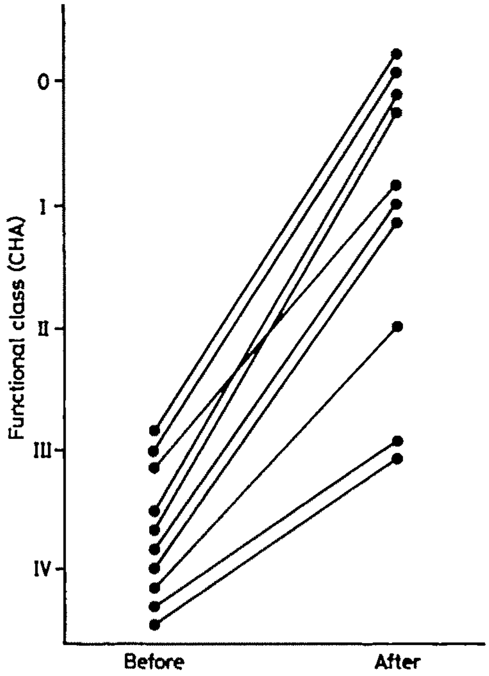


Fig 3 *Functional class (Canadian Heart Association classification, CHA) of 10 surviving patients before and after angioplasty.*

via the femoral approach in 10 patients.[4] Their technique included the use of a specially constructed guide wire placed deeply into the internal mammary artery over which they advanced a tapered guiding catheter. Our experience with a more straightforward technique was similarly successful. We support their advice to use ultralow profile balloons, which enabled easy passage of catheters through even the most tortuous internal mammary arteries and permitted the crossing of tight stenoses.

Caution should be exercised when positioning the guiding catheter in the ostium of the internal mammary artery to avoid dissection of this fragile vessel.[2 12 13] If serious difficulty is encountered in maintaining a stable position of the guiding catheter, then the ipsilateral brachial artery approach seems to be a reasonable alternative, particularly when dilatation of right internal mammary artery grafts is attempted, because this may be more difficult from the groin.

Percutaneous transluminal angioplasty of mammary artery grafts seems to be both safe and successful and to result in an excellent improvement in symptoms. The relatively simple technique that we have described with the use of standard equipment and the currently available guiding catheters should provide an effective means for experienced angioplasty centres to treat patients presenting with stenoses of internal mammary artery grafts.

MRB is a recipient of an Overseas Research Fellowship from the South Australian Lions Heart Research Foundation.

References

1 Kussmaul WG III. Percutaneous angioplasty of coronary bypass grafts: an emerging consensus. *Cathet Cardiovasc Diagn* 1988;15:1–4.
2 Dorros G, Lewin RF. The brachial artery method to transluminal internal mammary artery angioplasty. *Cathet Cardiovasc Diagn* 1986;12:341–6.
3 Cote G, Myler RK, Stertzer SH, *et al.* Percutaneous transluminal angioplasty of stenotic coronary artery bypass grafts: 5 years' experience. *J Am Coll Cardiol* 1987;9:8–17.
4 Pinkerton CA, Slack JD, Orr CM, VanTassel JW. Percutaneous transluminal angioplasty involving internal mammary artery bypass grafts: a femoral approach. *Cathet Cardiovasc Diagn* 1987;13:414–8.
5 Salinger M, Drummer E, Furey K, Bott-Silverman C, Franco I. Percutaneous angioplasty of internal mammary artery graft stenosis using the brachial approach: a case report. *Cathet Cardiovasc Diagn* 1986;12:261–5.
6 Loop FD, Lytle BW, Cosgrove DM, *et al.* Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. *N Engl J Med* 1986;314:1–6.
7 Spencer FC. The internal mammary artery: the ideal coronary bypass graft? *N Engl J Med* 1986;314:50–1.
8 Grondin CM, Campeau L, Lespérance J, Enjalbert M, Bourassa MG. Comparison of late changes in internal mammary artery and saphenous vein grafts in two consecutive series of patients 10 years after operation. *Circulation* 1984;70 (suppl 1):208–12.
9 Kay HR, Korns ME, Flemma RJ, Tector AJ, Lepley D Jr. Atherosclerosis of the internal mammary artery. *Ann Thorac Surg* 1976;21:504–7.
10 Sims FH. A comparison of coronary and internal mammary arteries and implications of the results in the etiology of arteriosclerosis. *Am Heart J* 1983;105:560–6.
11 Bashour TT, Hanna ES, Mason DT. Myocardial revascularization with internal mammary artery bypass: an emerging treatment of choice. *Am Heart J* 1986;111:143–51.
12 Farooqi S, Jain AC, O'Keefe M. Catheter-induced left internal mammary artery bypass graft dissection. *Cathet Cardiovasc Diagn* 1985;11:597–601.
13 Giorgi LV, Hartzler GO, McConahay DR, Rutherford BD, Johnson WL. PTCA of distal coronary stenosis via patent internal mammary artery grafts: improved recent experience [Abstract]. *J Am Coll Cardiol* 1986;7:105A.

Br Heart J 1989;61:421–5

A new exercise test for the assessment of heart failure: use of a self powered treadmill

J PARAMESHWAR, J-H E DAMBRINK, J SPARROW, C WRIGHT, A PARK, J TWEED, P A POOLE-WILSON

From the National Heart and Lung Institute and National Heart and Chest Hospitals, Dovehouse Street, London

SUMMARY Time limited exercise on a self powered treadmill was evaluated as a method of assessing functional capacity in patients with mild heart failure. The characteristics of the treadmill were established by exercising 11 controls at three speeds and two inclinations and comparing oxygen consumption with that on a motorised treadmill under the same conditions. Oxygen consumption on the self powered treadmill at an equivalent speed and inclination was significantly higher because of the work needed to overcome the friction of the belt. Unlike a conventional treadmill, increasing the gradient on the self powered treadmill did not increase oxygen consumption. The distance walked in 12 minutes on the self powered treadmill was measured in eight patients with mild heart failure and ten controls. Maximal oxygen consumption was measured in the same group on a conventional treadmill by a mass spectrometer. There was a significant correlation between the distance walked and maximum oxygen consumption.

In patients with mild heart failure the distance travelled in 12 minutes on a self powered treadmill provides a practical, inexpensive, and sensitive method of assessing functional capacity.

The measurement of respiratory gas exchange during a maximal exercise test is established as an objective and reproducible method of assessing exercise capacity in patients with heart failure.[1-3] The method is not widely available because the equipment is expensive and the procedure needs staff, training, and time. The end points are not entirely objective although knowledge of the maximum oxygen consumption and the respiratory ratio at peak exercise greatly ease the interpretation of an exercise test. Maximal exercise testing can be unpleasant for patients and worrying to doctors.

The six minute walking test was devised as an inexpensive and simple alternative method of assessing exercise capacity.[4 5] The maximum distance that patients can walk along a flat corridor in six minutes at a self selected speed is measured. The distance walked in a given time, rather than the maximum level of exercise that can be achieved, may relate more closely to a patient's symptoms, be more relevant to limitations of everyday activities, and may be more acceptable to patients.

The distance walked during a six minute walking test has been shown to discriminate better than measurement of maximal oxygen consumption between patients with severe chronic heart failure. In contrast the variation in the distance walked by patients with mild heart failure was small compared with the differences in maximum oxygen consumption.[5] We report here a study of time limited exercise on a self powered treadmill as an alternative method that does not need a corridor. The objectives were threefold: firstly, to establish the characteristics of the treadmill in terms of oxygen consumption; secondly, to determine whether and how the distance walked related to maximum oxygen consumption; and thirdly, to measure oxygen consumption during the walking test.

Patients and methods

We studied 11 controls (mean age 32, range 25–44 years) and eight patients with mild or moderate heart failure (mean age 64, range 52–73 years). The controls were believed to be free of cardiac disease. The cause of heart failure was coronary artery disease in six patients and uncertain in two. The mean

Requests for reprints to Dr J Parameshwar, National Heart Hospital, Westmoreland Street, London W1M 8BA.

Accepted for publication 24 January 1989

duration of heart failure was five years (range 2–13 years). All the patients were on a loop diuretic (mean dose of frusemide 55 mg). Four patients were taking amiloride. No patient was taking an angiotensin converting enzyme inhibitor. One patient was in atrial fibrillation and was receiving digoxin to control the heart rate. The mean maximum oxygen consumption of patients was 20·5 ml/kg/min. Exclusion criteria were evidence of myocardial ischaemia on exercise testing, significant pulmonary disease, or inability to exercise for any reason other than dyspnoea or fatigue. No patient had chest pain or any change on the electrocardiogram during or after exercise.

The study groups exercised on a Tunturi Jogger 2 self powered treadmill. This consists of a conveyer belt that slides over an underplate by the force of the subject walking on the belt. A liquid crystal display can show the distance travelled, the current speed, or the time elapsed, or will scan between these three. The distance walked was also recorded by a Trumeter surveyor's wheel attached to the belt of the treadmill. Both controls and patients practised on the treadmill before the study started. Most patients had performed the test at least five times before the study.

The oxygen consumption of 11 controls was measured at gradients of 4·4% and 11·1% (4° and 10° respectively). Subjects walked at 3, 5, and 7 km/h. Each stage lasted three minutes, giving a total of nine minutes of continuous exercise. Similar measurements of oxygen consumption were made on a conventional motorised treadmill at a gradient of 11·1% and at the same three speeds.

Ten controls and the eight patients were asked to walk for 12 minutes on the Tunturi treadmill, set at a gradient of 6·7% (6°). All were asked to walk the greatest distance possible at any speed they chose. The distance walked was recorded. Oxygen consumption and carbon dioxide production were monitored throughout the test.

We measured maximum oxygen consumption on a conventional treadmill (Bruce protocol) by an argon dilution technique and a mass spectrometer.[16] The anaerobic threshold and extrapolated maximum consumption were obtained by computerised analysis with a curve fitting model.[17]

Results are expressed as mean (SD). Differences were analysed by analysis of variance and Student's *t* test.

Results

COMPARISON BETWEEN GRADIENTS ON THE SELF POWERED TREADMILL

All the controls reported greater difficulty walking on the self powered treadmill at a gradient of 4·4% than at 11·1%. Only five completed nine minutes of exercise at both gradients; 10 completed six minutes at 4·4%, and all 11 did so at 11·1% (fig 1). At 4·4% the mean oxygen consumption was 23·4 (3·0), 32·8 (3·9), and 41·1 (3·5) ml/kg/min at speeds of 3, 5, and 7 km/h respectively. At a gradient of 11·1% the corresponding values were 21·3 (2·2), 30·5 (3·7), and 40·7 (3·3) ml/kg/min respectively. This difference was significant at 3 km/h (p < 0·02) but not at higher speeds.

At the two lower speeds (3 and 5 km/h) and at a slope of 4·4% the oxygen consumption correlated inversely with weight of the controls (r = −0·83, p < 0·002 and r = 0·75, p < 0·01). No correlations were apparent under any other conditions studied.

COMPARISON BETWEEN TREADMILLS

All the controls reported greater difficulty exercising on the self powered treadmill than on a conventional motorised one at comparable slopes and speeds. Ten completed nine minutes of exercise on the motorised treadmill. At a fixed gradient of 11 1% the mean oxygen consumption on the conventional treadmill was 16·4 (2·0), 21·9 (2·1), and 27·1 (2·0) ml/kg/min at 3, 5, and 7 km/h respectively (fig 1). This was significantly less than the corresponding values on the self powered treadmill at all speeds (p < 0·001).

MAXIMAL OXYGEN CONSUMPTION

Maximal oxygen consumption was limited by symptoms in patients and controls. The mean maximal oxygen consumption was 40 9 (11·3) ml/kg/min in the controls and 20 5 (4·1) ml/kg/min in the patients. The mean extrapolated maximal oxygen consumption[7] was 45·1 (13·1) ml/kg/min and 26 (5·7) ml/kg/

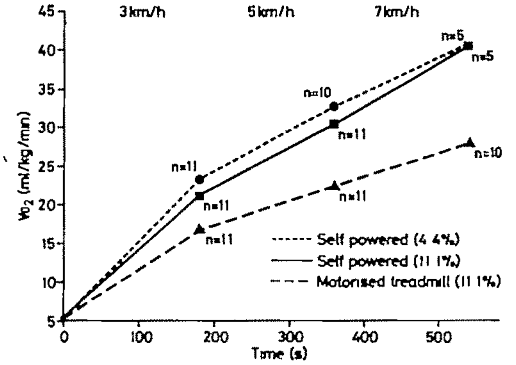


Fig 1 *Oxygen consumption in controls after three minutes of exercise on the self powered treadmill at speeds of 3, 5, and 7 km/h. Not all subjects were able to exercise at the highest speed. For comparison the oxygen consumption on the motorised treadmill under similar conditions is shown.*

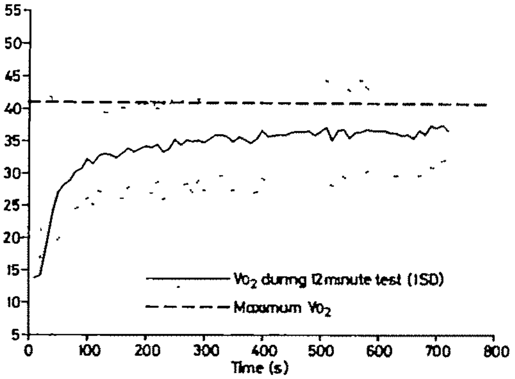


Fig 2 *Oxygen consumption during the 12 minute walking test on the self powered treadmill in 11 controls. For comparison the maximum oxygen consumption of the group is also shown.*

min respectively. The mean anaerobic threshold was 25 (4·9) ml/kg/min in the controls and 17·3 (4·7) ml/kg/min in the patients. The mean respiratory quotient at peak exercise was 1·14 in controls and 1·06 in patients.

TWELVE MINUTE WALKING TEST

The mean distance walked in twelve minutes was 1052 (195) m in ten controls and 550 (108) m in the eight patients. The difference was significant ($p < 0{\cdot}001$). During the test, oxygen consumption in patients and controls reached a plateau after approximately three minutes of exercise. This plateau value was 84% of the maximal oxygen consumption in the patients and 89% in controls (figs 2 and 3). The respiratory quotient at the end of the test was 1·03 in controls and 0·97 in patients. The respiratory quotient varied during the test and the value at the end of the test may be higher than during the test because of an attempt to walk faster in the last few moments of the test. The distance walked in 12 minutes correlated with maximal oxygen consumption in controls ($r = 0{\cdot}85$, $p < 0{\cdot}005$) and in the patients ($r = 0{\cdot}75$, $p < 0{\cdot}05$). When the results for the two groups were combined the correlation was highly significant ($r = 0{\cdot}94$, $p < 0{\cdot}0001$) (fig 4). The extrapolated maximal oxygen consumption correlated with the distance walked in 12 minutes in the controls ($p < 0{\cdot}01$) but not in the patients. When the results for the two groups were combined the correlation was significant ($r = 0{\cdot}89$, $p < 0{\cdot}001$). The anaerobic threshold did not correlate with the distance walked in either group. There was also no correlation in either group between the distance walked in 12 minutes on the self powered treadmill and the exercise time on the conventional treadmill.

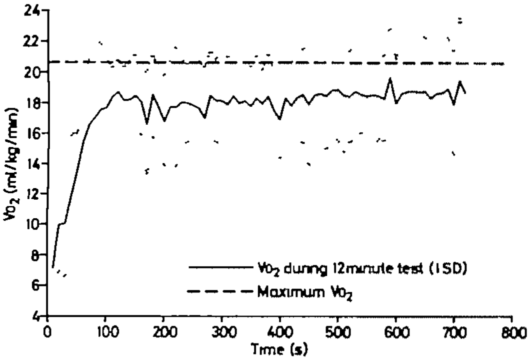


Fig 3 *Oxygen consumption during the 12 minute walking test on the self powered treadmill in eight patients with mild heart failure. For comparison the maximum oxygen consumption of the patients is also shown.*

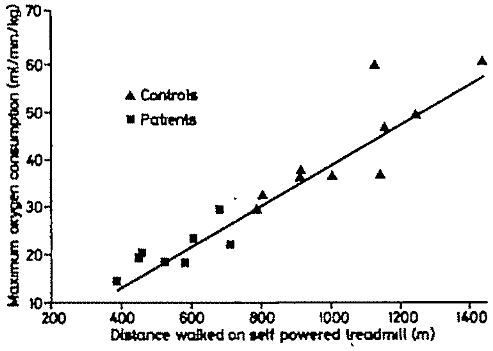


Fig 4 *Maximum oxygen consumption determined from a standard exercise test and plotted against the distance walked in 12 minutes on the self powered treadmill in patients with mild heart failure and in controls ($r = 0{\cdot}85$, $p < 0{\cdot}005$ in controls, $r = 0{\cdot}75$, $p < 0{\cdot}05$ in patients, $r = 0{\cdot}94$, $p < 0{\cdot}0001$ for all persons).*

Discussion

Symptoms, often assessed by the New York Heart Association criteria for breathlessness, are a poor guide to the severity of heart failure[8 9] and in recent years exercise testing has been widely used to classify patients with heart failure, to follow the progression of heart failure, and to assess the efficacy of new treatments. Despite this widespread use of exercise testing, particularly in clinical trials of drugs,[10] there is no agreement on the most appropriate protocol or how to interpret the results. To circumvent the variability and subjectivity of the simple measurement of exercise duration, analysis of gas exchange during exercise and at peak exercise has become popular. Maximal oxygen consumption and anaerobic threshold are believed to provide more objective and reproducible end points. A knowledge of the respiratory quotient at peak exercise establishes whether the patient was truly limited by the cardiovascular system.[1 11 12] The equipment necessary to analyse respiratory gas exchange is expensive, however, and its use requires considerable technical skill. For these reasons the method is limited to a few centres. A more fundamental criticism of the method is that the relation between maximum exercise capacity and either symptoms or the ability to perform the common tasks of everyday life is not established.

The six minute walking test was put forward as an alternative test to assess patients with mild heart failure, which is cheap, reproducible, and easy to perform in most circumstances. The test measures the maximum distance a patient can walk at a self selected speed along a flat corridor in six minutes. Since the patient chooses the speed of walking the test may be more typical of normal activity than a conventional maximum exercise test. A major drawback to the test is that it does not appear to discriminate between patients with mild heart failure and normal subjects.[5] Also a long corridor is required.

We modified the six minute walking test by extending the time to 12 minutes and by using a self powered treadmill rather than a corridor. The treadmill is convenient to use, allows better supervision of the patients, and is inexpensive and safe. The treadmill, however, is not simply a replacement for the corridor. The slope can be adjusted and considerable work is required to overcome the friction of the belt and inertia of the rollers. Thus it is a more strenuous test. The importance of these factors was not initially appreciated although we did expect that an increase of work on the treadmill might make the test more sensitive in patients with mild heart failure. The results in controls show that oxygen consumption was higher than on a motorised treadmill at all speeds by up to 15 ml/kg/min (fig 1). The oxygen consumption did not increase on the self powered treadmill as the slope was increased from 4·4° to 11·1°. The reason for this observation is that overcoming the friction of the belt requires considerably less effort at the higher slope because body weight is more effective. The reduction in work required to overcome the friction of the belt must offset the greater oxygen consumption of walking up a steeper slope. At the lower slope and speeds body weight correlated inversely with oxygen consumption expressed per kg body weight. This was probably because heavier people were more effective in overcoming the friction of the belt under these conditions.

The mean maximum oxygen consumption of the patients was 20·5 ml/kg/min, indicating mild to moderate heart failure.[1] There was a significant difference in the distance walked in twelve minutes by the patients and controls. Although the controls were not age matched it is unlikely that their younger ages alone accorded for the large difference in the distance walked. Maximum oxygen consumption in a normal population of the same age as our patients is 33 ml/kg/min[13] compared with the value in our controls of 40·9 ml/kg/min and 20·5 ml/kg/min in the patients. The distance walked correlated with the maximum oxygen consumption in patients, in controls, and in the total study group. The relation seemed to be linear (fig 1). Patients walked approximately half the distance of controls. There is, therefore, a substantial potential for a detectable improvement in response to treatment.

The correlation between extrapolated maximal oxygen consumption[7] and the distance walked in 12 minutes on a self powered treadmill was significant for controls but not for patients. The anaerobic threshold was originally introduced as an objective measure of a person's exercise capacity.[14] In the present study the anaerobic threshold did not correlate with the distance walked in the 12 minute walking test. This is probably because of inaccuracies in calculating the anaerobic threshold. Indeed the whole concept and existence of an anaerobic threshold can be challenged.[7] No correlation was found between exercise time on a conventional treadmill and the distance walked during the 12 minute walking test. This finding is initially surprising but may reflect the many factors that determine exercise time on a motorised treadmill and account for differences between maximum oxygen consumption and exercise time. These include muscle mass, body weight, training effects, walking methods[15] and muscle fibre type in different people. Another factor is the curvilinear relation between work performed and time on a motorised treadmill when a Bruce protocol is followed.

The distance travelled during a time limited exercise test will depend on the ability of the subject to pace himself optimally. In general, subjects were able to pace themselves appropriately. Oxygen consumption during the test reached a plateau in both controls and patients (figs 2 and 3). People in both groups took approximately three minutes to reach a steady state of oxygen consumption. There was a small increase of oxygen consumption in the last few seconds of the test that was particularly noticeable in normal people. This represented their final effort to increase the distance walked as the end of the test approached. Patients tended to walk at an oxygen consumption nearer to their maximum than controls; the difference was not large (figs 2 and 3).

The major difficulty in evaluating any new test for assessing patients with heart failure is that there is no absolute standard or measure of heart failure with which to compare the test. Haemodynamic variables at rest or exercise are known not to correlate with symptoms or exercise capacity. Measures of quality of life have the advantage of being a logical approach but they also reflect biases in the designer of the questionnaire, are subjective, and are difficult, if not impossible, to validate. This accounts for the interest in exercise testing to assess patients with heart failure. The test that we describe has important advantages over other exercise protocols. It is easy to perform, mimics normal activity, is cheap, presents a reasonable challenge to the patient, is acceptable to the patient, and has the sensitivity to detect improvement. The test seems particularly well suited to patients with mild or moderate heart failure but less practical in severe heart failure because of the effort needed to overcome the friction of the belt. None the less, the test may be useful in patients with severe heart failure because they can choose their own speed of walking.

We arbitrarily chose 12 minutes for the duration of the test believing that it was a suitable time over which to assess a patient without other factors such as loss of concentration contributing to the outcome. With hindsight we think that the test could have been shortened to nine minutes. A six minute test may be insufficient to establish a steady rate of exercise. The test may be suitable not only for patients with mild or moderate heart failure but also for patients with severe heart failure.

We thank Stuart Pharmaceuticals for the purchase of the Tunturi treadmill.

References

1 Lipkin DP, Perrins J, Poole-Wilson PA. Respiratory gas exchange in the assessment of patients with impaired ventricular function. *Br Heart J* 1985;54:321–8.

2 Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilisation and ventilation during exercise in patients with chronic cardiac failure. *Circulation* 1982;65:1213–23.

3 Wilson JR, Fink LI, Ferraro N, Dunkman WB, Jones RA. Use of maximal bicycle exercise testing with respiratory gas analysis to assess exercise performance in patients with congestive heart failure secondary to coronary artery disease or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1986;58:601–6.

4 Guyatt GH, Sullivan MJ, Thompson PI, *et al.* The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985;132:919–23.

5 Lipkin DP, Scriven AJ, Crake T, Poole-Wilson PA. Six minute walking test for assessing exercise capacity in chronic heart failure. *Br Med J* 1986;292:653–5.

6 Davies N, Dennison DM. Measurement of metabolic gas exchange and minute volume by mass spectrometry alone. *Respir Physiol* 1979;36:261–7.

7 Buller NB, Poole-Wilson PA. Extrapolated maximum oxygen consumption: a new method for the objective analysis of respiratory gas exchange during exercise. *Br Heart J* 1988;59:212–7.

8 Lipkin DP. The role of exercise testing in chronic heart failure. *Br Heart J* 1987;58:559–66.

9 Weber KT, Janicki JS. Cardiopulmonary exercise for evaluation of chronic heart failure. *Am J Cardiol* 1985;55:22A–31A.

10 Lipkin DP, Poole-Wilson PA. Treatment of chronic heart failure: a review of recent trials. *Br Med J* 1985;291:993–6.

11 Franciosa JA. Exercise testing in chronic congestive heart failure. *Am J Cardiol* 1984;53:1447–50.

12 Wasserman K, Whipp BJ, Koyal SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. *J Appl Physiol* 1973;35:236–43.

13 Astrand P-O, Rodahl K. *Textbook of work physiology.* New York: McGraw-Hill, 1970

14 Wasserman K, McIlroy MB. Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. *Am J Cardiol* 1964;14:844–52.

15 Froelicher VF. Exercise testing and training: clinical applications. *J Am Coll Cardiol* 1983;1:114–25.

Br Heart J 1989;61:426–31

Effect of temperature on rate of left ventricular pressure fall in humans

RICHARD A LUKE,* CHARLES E GILLBE,† ROBERT S BONSER,‡
MATTHIAS PANETH,† DAWN SOMERSET,* JUDITH THOMAS,‡
DEREK G GIBSON*

*From the Departments of *Cardiology, †Anaesthetics, and ‡Cardiac Surgery, Brompton Hospital, London*

SUMMARY The time constant (T) of left ventricular pressure fall is widely used as an index of ventricular "relaxation". It is not known whether its rate limiting step is deactivation, an enzymic energy consuming reaction whose rate is therefore sensitive to temperature, or elastic recoil. To distinguish between these possibilities, the time constant was measured by simple logarithmic (Tlog) and exponential (Texp) methods in 12 patients during cooling before coronary artery grafting. Ventricular loading conditions were altered by transfusion from bypass to maintain arterial and left atrial pressures constant in individual patients, though heart rate fell from 86 (8·4) to 68 (10) beats/min. Tlog increased from 49 (10) ms mean (SD), at 37°C to 86 (15) ms at 31°C, and Texp from 63(14) at 37°C to 112 (23) ms at 31°C with intermediate values at 34°C. Texp proved sensitive to "noise" at low temperatures, but the overall change in Tlog with temperature was 9% per °C—considerably less than that observed experimentally for the rate of tension decline of isolated myocardium, and possibly itself an overestimate because of the concomitant fall in heart rate.

The relatively small effect of temperature on Tlog in humans, associated with a considerable load sensitivity appearing under hypothermic conditions, does not favour simple dependence on deactivation as the rate limiting step of left ventricular pressure fall, but suggests that its determinants may be complex.

Though the time constant (T) of left ventricular pressure fall during isovolumic relaxation is widely used as an index of ventricular relaxation and of diastolic function,[1-3] underlying mechanisms in humans have not been defined in detail. Since it depends on events occurring before mitral valve opening, it is not directly affected by left ventricular filling, and is thus likely to reflect either the rate of termination of the active state within the myocardium—that is deactivation—or elastic restoring forces, possibly accompanied by a change in left ventricular cavity shape. Ventricular deactivation is a process requiring energy and so its rate is temperature sensitive.[4 5] When cardiopulmonary bypass is initiated before coronary artery surgery the heart is cooled; this provides an opportunity to assess the effect of temperature on early diastole. We therefore aimed to determine how myocardial temperature changes affected the time course of left ventricular pressure fall to help to understand clinical disturbances seen in humans.

Patients and methods

We studied eleven men and one woman (aged 42–65) undergoing coronary artery surgery for relief of angina pectoris. We excluded those with unstable angina, clinically significant left main stem stenosis, associated valve disease, or impaired left ventricular function (ejection fraction <50%). The resting preoperative electrocardiogram was normal in eight and showed inferior Q waves in four. At operation, between two and five grafts were attached. The protocol was approved by the ethics committee of the National Heart and Chest Hospital, with the requirement that data collection should be complete within 30 minutes. All patients gave witnessed informed consent and there were no complications.

Requests for reprints to Dr Derek G Gibson, Cardiac Department, Brompton Hospital, London SW3 HP

Accepted for publication 10 January 1989

ANAESTHETIC TECHNIQUE

All patients were premedicated with papaveretum 10–20 mg and hyoscine 0 2–0·4 mg. The left radial artery was cannulated under local anaesthesia and arterial pressure was monitored continuously before and throughout induction. General anaesthesia was induced with fentanyl 8 μg/kg. Pancuronium 0·1–0·15 mg/kg was administered to obtain neuromuscular blockade. Anaesthesia was maintained by intermittent positive pressure ventilation with air, oxygen, and isoflurane 1–2%.

SURGICAL TECHNIQUE

After sternotomy, cardiopulmonary bypass was established with right atrial drainage and return to the ascending aorta. A 5F Millar catheter with pressure tip transducer (Millar Instruments model SPC-350, with a temperature coefficient of less than ±1 mm Hg between 23 and 38°C) was then introduced into the left ventricle through an apical vent incision. A 16 gauge cannula was inserted into the left atrium and connected to a fluid filled pressure transducer. We used this to monitor the left atrial pressure. Myocardial temperature was measured by a temperature probe (YSI series 500, no 586) inserted into the posterior left ventricular wall. In the first five patients, the septal temperature was also monitored with a hypodermic probe (YSI, series 500, no 513, 20 gauge). Because it was identical with that of the posterior wall within five minutes of a change in temperature in all these cases we did not continue to measure the temperature of the septum in subsequent patients. The heart was rewarmed if necessary to the normothermic range (36·5 to 37·5° C) and bypass discontinued with a mean left atrial pressure of 2–6 mm Hg, or higher if arterial pressure appeared inadequate. After five minutes of equilibrium, left ventricular pressure was recorded and simultaneous mean left atrial pressure and myocardial temperature were noted. The filling pressure was then increased by transfusion from the bypass up to a maximum of 15 mm Hg in order to increase arterial pressure by 20% or more. A second set of recordings was obtained after one minute. Bypass was then resumed, and the heart was cooled to the hypothermic range (31 to 32·5°C), and further recordings were obtained at two filling pressures as for the normothermic range. An additional set of recordings was made at an intermediate temperature when possible within the time constraints of the protocol. There was no electrocardiographic evidence of left ventricular ischaemia at any time during the study.

CALIBRATION AND RECORDINGS

The Millar catheter was immersed in saline for at least 20 minutes before use to minimise zero drift and was then calibrated electrically. Zero pressure was taken as atmospheric. At the end of the study, drift was less than 2 mm Hg for all patients. Left ventricular pressure was recorded on tape and a hard copy obtained by a photographic recorder working at effective paper speeds of 50 and 200 mm/s (Meddars model 1100 with LS-8 recorder, Honeywell, fig 1). Zero left atrial pressure was taken at the mid-atrial level. Temperature probes were individually precalibrated.

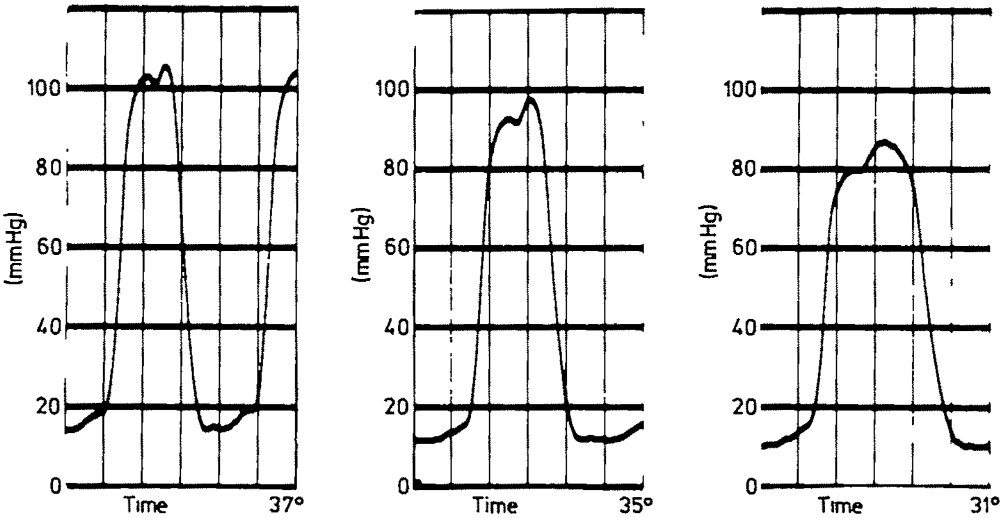


Fig 1 *Effect of temperature on the left ventricular pulse at 37°C (left panel), 35°C (centre panel), and 31°C (right panel).*

STATISTICAL ANALYSIS

Because values of T might have been affected by varying loading conditions, arterial and left atrial pressures were matched as closely as possible at different temperature levels within individual patients. Left ventricular pressure recordings were digitised every 5 ms. We took isovolumic relaxation as the interval from the time of peak negative dP/dt until ventricular pressure was 5 mm Hg above the end diastolic pressure of the preceding beat, and analysed data points only during this period. We determined peak left ventricular and mean left atrial pressures directly from the appropriate recordings.

We calculated the time constant of relaxation (Tlog) by the semilogarithmic method originally suggested by Weiss *et al*,[6] according to the function $P = Poe - \frac{t}{T}$, where Po is pressure at zero time—that is simultaneous with dP/dt—P the pressure at any time (t) after this, and T the time constant of pressure fall. This derivation assumes that the asymptote (Pb) of pressure fall is zero, and is measured from a plot of the natural logarithm of pressure against time. For all recordings, the correlation coefficient of this plot, using a linear fit, was greater than 0·98. We also calculated the time constant from the plot of negative dP/dt against P. This method gives T as the slope of the line, and the asymptote is derived from the intercept.[7] When pressure fall was prolonged at low temperatures, dP/dt was subject to "noise"; and we did not use values whose correlation coefficient fell below 0·90 in subsequent analysis.

We used average values for two beats and, for the purpose of analysis, the three temperature ranges defined in the experimental protocol were considered: normothermic (above 36°C), intermediate (33–36°C), and hypothermic (<33°C).

Preoperative left ventricular angiograms were digitised frame by frame[8] to determine ejection fraction and regional wall motion in nine patients. In three patients angiograms were technically unsuitable for such analysis because of extrasystoles but left ventricular function seemed to be unimpaired on visual assessment.

Results

HAEMODYNAMIC VARIABLES

Heart rate fell with temperature from a mean value of 86 (8·4) beats per minute in the range 35–37°C to 77 (9·5) beats per minute in the intermediate temperature range, and 68 (10) beats per minute at the lowest range, between 31 and 33°C. The relation between heart rate and temperature was consistent, and given by the regresssion equation:

Heart rate = 3·78 (temperature) − 55 beats/min,

with a correlation coefficient of 0 69 ($p < 0{\cdot}001$), and a standard error of the estimate of 9·8 beats/min.

At normal temperature, peak arterial systolic pressure was 105 (15) mm Hg with a mean atrial pressure of 8 (3) mm Hg, compared with 106 (15) and 9 (4) mm Hg, respectively, in the intermediate range, and 104 (15) and 9·5 (4·5) mm Hg at the lowest temperatures. There was no significant difference between these values at the three temperature ranges. Negative dP/dt depended on both temperature and peak systolic pressure, as given by the multiple regression equation:

Peak negative dP/dt = −2550 + 71 (temperature) − 10 (systolic pressure), where $r = 0{\cdot}87$ and $p < 0{\cdot}001$ for both predictors.

TIME CONSTANTS

Above 36°C.—Mean values of Tlog and Texp were 49 (10) and 63 (14) ms respectively. In patients studied under normothermic conditions, the correlation coefficient of the relation between Tlog and heart rate was −0·59, and that between Texp and heart rate was −0·33. Neither was statistically significant ($p < 0{\cdot}10$ and 0·20, respectively).

Temperature 33–36°C.—Mean values of Tlog and Texp increased to 72 (11) and 87 (20) respectively; these values were significantly longer than those recorded in the normothermic range ($p < 0{\cdot}01$).

Temperature <33°C.—The mean value of Tlog was further prolonged to 86 (15) ms. Because of "noise" associated with the trace of dP/dt at lower temperatures, only four data pairs could be calculated for Texp, whose mean value was 112 (23) ms. When values obtained under intermediate or hypothermic conditions (that is below 36°C) were considered, again the correlation between Tlog and spontaneous heart rate was not significant ($r = -0{\cdot}28$). Overall, the relation between Tlog and temperature was given by the equation:

Tlog = 330 − 7·7 (temperature),

with a correlation coefficient of −0·87 ($p < 0{\cdot}001$) and standard error of the estimate 34 ms (fig 2). Directionally similar changes were seen in Texp, but their statistical significance could not be calculated because only four values were available in the low temperature range.

ASYMPTOTE OF PRESSURE FALL

The asymptote of pressure fall can be calculated as the pressure at which dP/dt becomes zero. The mean value of Pb at normal temperatures was −12 (12) mm Hg, −9 (7) at intermediate, and −15

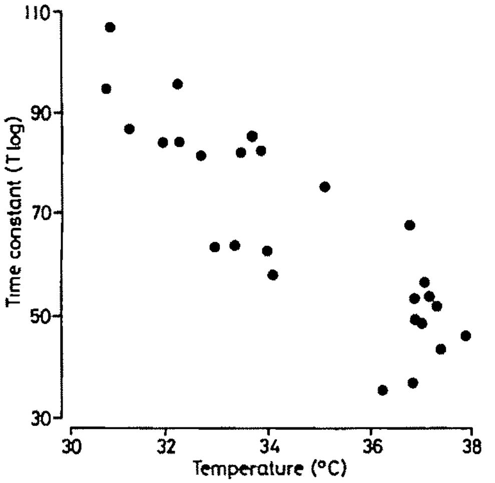


Fig 2 *Relation between myocardial temperature and Tlog during myocardial cooling.*

(13) mm Hg at the lowest temperatures. These values all differed significantly from zero ($p < 0.01$), but were unrelated to temperature.

ANALYSIS OF ANGIOGRAMS

Angiograms adequate for analysis were obtained in nine patients. The ejection fraction ranged from 57% to 84%. Contour displays showed a completely normal pattern of regional wall motion in three. The pattern of "diagonal contours"[9] for the apical or inferior segment was present in five, without any other abnormality in four of these and with inferior hypokinesis in one. In one patient, there was a change in cavity shape during isovolumic relaxation, with early outward motion of the anterior wall, and delayed inward motion along the inferior wall.

Discussion

Although the time constant (T) of relaxation is widely used to assess the left ventricle during diastole in humans, little is known of what determines its length in individual patients. Problems in interpreting it are compounded by inconsistent definitions. In the intact heart, the word "relaxation" has been used to mean deactivation,[10] outward ventricular wall motion or wall thinning,[11] and even a return to precontractile configuration.[12] Not only are these various definitions mutually incompatible, but they include isovolumic relaxation and all three phases of ventricular filling. Even if the mechanism of ventricular pressure fall were completely understood, it would still not be clear which of these various processes the time constant actually assesses.

Measuring a time constant of pressure fall in the intact heart presents obvious technical difficulties. Early experiments showed that tension decayed exponentially in isolated muscle,[13] and so could be quantified as a rate constant. Weiss *et al* proposed that Tlog, calculated from a semilogarithmic plot of ventricular pressure, could be used in a similar way to follow relaxation in the intact heart[6]—assuming that the pressure fall was exponential, the ventricle isovolumic, and the asymptote zero. More recent methods for calculating T have shown that the asymptote is not zero,[1,7] but is frequently large and negative. There is no theoretical reason why pressure fall should be exponential during isovolumic relaxation, particularly in disease, and striking departures have been noted in hearts damaged by ischaemia or with severe left ventricular hypertrophy.[14] Our patients had normal or near normal patterns of left ventricular wall motion before operation, and showed no evidence of acute ischaemia at the time that measurements were made. Correlation coefficients for calculation of Tlog were greater than 0·98 throughout the study; this indicates that assuming an exponential was probably not a major source of error. Calculation of Texp at low temperatures was, however, affected by "noise" on the dP/dt trace rather than by any configurational change in left ventricular pressure fall, but this method did allow us to show that values of the asymptote were consistently subatmospheric. It has been suggested that the asymptote may differ from zero simply because pericardial or intrathoracic pressure are sub-atmospheric.[15] Although the values we obtained when the chest and pericardium were open were less negative than those previously reported at cardiac catheterisation,[1] they were consistently below zero, suggesting that factors other than pericardial or intrathoracic pressure contribute to the asymptote of left ventricular pressure fall in intact man.

A second problem in calculating T is to define the time of mitral valve opening. We used the simple criterion of taking the time when left ventricular pressure was 5 mm Hg above end diastolic pressure. Other criteria have been used, including arbitrary points on the pressure curve, at[3,6,16] or above[15,17,18] the end diastolic pressure of the previous beat, pressure crossover,[7] or the time of mitral valve opening determined by angiography[2] or echocardiography.[12] In patients with ventricular disease, when left atrial pressure is significantly raised, the isovolumic relaxation time may be short or even zero,[19] which invalidates the basis on which time constant is calculated.

Haemodynamic influences on T have been extensively studied. It is generally agreed that T shortens as the heart rate increases,[1,4,5] but the effect of arterial pressure is variable, with some studies reporting a lengthening of T as systolic pressure increases[16,17,20] and others no change.[5,21,22] Any influence of filling pressure[17] is probably indirect and due to its effect on arterial pressure.[15] The use of different anaesthetic agents has been invoked as a cause of these discordant experimental results.[17] Isoflurane is known to cause vasodilatation, depress contractility, and possibly to inhibit slow calcium channels[23]; but it seems unlikely that it influenced our results to any significant extent since the level of anaesthesia was maintained constant throughout the procedure. If T does indeed reflect early diastolic processes, therefore, it is likely to be load dependent,[12,24] so that in the present study we matched values of arterial and left atrial pressures at different temperatures in individual patients.

The rate limiting step of left ventricular pressure fall in humans is still uncertain. During isovolumic relaxation, it presumably reflects the effects either of deactivation or of elastic restoring forces, though their relative preponderance has not been established. Decay of the active state is associated with calcium uptake into the sarcoplasmic reticulum. Because this is an enzymic process requiring energy,[4,5] its rate will be very sensitive to temperature—values of 17% per degree centigrade in the rate of tension fall in isolated myocardium have been shown experimentally in the range 28–33°C.[25] Alternatively, restoring forces[26–28] residing in elastic elements within the myocardium and energised during the previous systole may determine the time course of left ventricular pressure fall. The effect of temperature on this mechanism would be significantly less than that on an enzymic process, although not absent altogether, because viscosity changes with temperature.[29]

Cooling the myocardium during cardiopulmonary bypass provides an excellent opportunity to investigate these possibilities in humans within a temperature range of approximately 7°C. Clearly, normal hearts cannot be studied in this way, but we selected patients with normal ventricular function judged in terms of ejection fraction and regional systolic and diastolic wall motion. The range of values of Texp at normal temperatures overlapped those previously reported at cardiac catheterisation in controls[1,18]; those of Tlog were a little longer, but this difference was almost certainly related to the less negative value of the asymptote in our patients studied with the chest open.[1] There was no evidence of acute ischaemia at the time that measurements were made. While minor differences between our results and those that would have been obtained in controls are expected, any residual effects of ischaemia are likely to have become smaller rather than larger as temperature fell, so it seems improbable that there were major discrepancies.

Our results confirm that the time constant of pressure fall was indeed somewhat prolonged with cooling in humans, amounting to approximately 9% per degree Centigrade. However, not only was this effect considerably less than that seen experimentally on the rate of tension decline, but, moreover, may actually be an overestimate. There was a consistent fall in heart rate in our patients, which would be expected per se to lengthen T, irrespective of any change in temperature. Although we were able to eliminate any overall dependence on heart rate in our patients, the possibility of an intrapatient effect remains. From the data of Thompson *et al*,[1] this fall in heart rate would be expected to increase Tlog by approximately 4 ms, or 10% of the total change between 38 and 32°C. Decreased catecholamine secretion,[30] and any direct effect of temperature on ventricular activation might also have been expected to prolong T indirectly. Finally, as we have briefly reported elsewhere,[31] values of T become very sensitive to arterial and venous pressure at temperatures below 34°C. This means that the effect of temperature itself becomes load dependent, being even further diminished as arterial pressure rises.

We conclude, therefore, that although the time constant of left ventricular pressure fall is prolonged with cooling in humans, the basis of this effect is complex. Its extent is considerably less than that in the rate of tension decline in isolated myocardium,[25] although the size of this discrepancy is difficult to quantify because load dependence develops in humans below 34°C. The results suggest that the rate of deactivation is not the only, or even a dominant, cause of the rate of pressure fall in man, and that underlying mechanisms are complex and multiple. We feel that it may be unwise to ascribe variation of the time constant of pressure fall in all circumstances to changes in any single entity, particularly one so loosely defined as "relaxation".

RAL was supported by a grant from the New Zealand Heart Foundation.

References

1 Thompson DS, Waldron CB, Juul SM, *et al.* Analysis of left ventricular pressure during isovolumic relaxation in coronary artery disease. *Circulation* 1982;65:690–7.

2 Fioretti P, Brower RW, Meester GT, Serruys PW. Interaction of left ventricular relaxation and filling during early diastole in human subjects *Am J Cardiol* 1980;46:197–203.

3 Katayama J, Kumada T, Fujii T, *et al.* Clinical charac-

teristics of left ventricular pressure decline during isovolumic relaxation in normal and diseased hearts. *Am Heart J* 1984;**107**:332–7.

4 Langer GA. Ion fluxes in cardiac excitation and contraction and their relation to myocardial contractility *Physiol Rev* 1968;**48**:708–75.

5 Nayler WG, Williams A. Relaxation in heart muscle: some morphological and biochemical considerations. *Eur Heart J* 1978;7(suppl).35–50.

6 Weiss JL, Fredericksen JW, Weisfeldt ML. Hemodynamic determinants of the time-course of fall in canine left ventricular pressure. *J Clin Invest* 1976;**58**.751–60.

7 Weisfeldt ML, Weiss JL, Frederiksen JT, Yin FCP. Quantification of incomplete left ventricular relaxation: relationship to the time constant for isovolumic pressure fall. *Eur Heart J* 1980;1:A119–29.

8 Gibson DG, Prewitt TA, Brown DJ. Analysis of left ventricular wall movement during isovolumic relaxation and its relation to coronary artery disease. *Br Heart J* 1976;**38**:1010–9.

9 Gibson DG, Greenbaum RA, Pridie RB, Yacoub MH. Correction of left ventricular asynchrony by coronary artery surgery. *Br Heart J* 1988;**59**:304–8.

10 Grossman W, McLaurin LP. Diastolic properties of the left ventricle. *Ann Intern Med* 1976;**84**:316–26.

11 Friedman MJ, Sahn DJ, Burris HA, Allen HD, Goldberg SJ. Computerized echocardiographic analysis to detect abnormal systolic and diastolic left ventricular function in children with aortic stenosis. *Am J Cardiol* 1979;**44**:478–86.

12 Brutsaert DL, Rademakers FE, Sys SU, Gillebert TC. Housmans PR. Analysis of relaxation in the evaluation of ventricular function of the heart. *Prog Cardiovasc Dis* 1985;**28**:143–63.

13 Parmley WW, Sonnenblick EH. Relation between mechanics of contraction and relaxation in mammalian cardiac muscle *Am J Physiol* 1969;**216**: 1084–91.

14 Rousseau MF, Verher C, Detry J-M, Brasseur L, Pouleur H. Impaired early left ventricular relaxation in coronary artery disease: effects of intracoronary nifedipine. *Circulation* 1980;**62**:764–72.

15 Gaasch WH, Carroll JD, Blaustein AS, Bing OHL. Myocardial relaxation: effects of preload on the time course of isovolumetric relaxation. *Circulation* 1986;73:1037–41.

16 Karliner JS, LeWinter MM, Mahler F, Engler R, O'Rourke RA. Pharmacologic and hemodynamic influences on the rate of isovolumic left ventricular relaxation in the normal conscious dog. *J Clin Invest* 1977;**60**:511–21.

17 Raff GL, Glantz SA. Volume loading slows left ventricular relaxation rate: evidence of load dependent relaxation in the dog heart. *Circ Res* 1981;**48**:813–24.

18 Carroll JD, Hess OM, Hirzel HO, Krayenbuehl HP. Dynamics of left ventricular filling at rest and during exercise. *Circulation* 1983;**68**:59–67.

19 Mattheos M, Shapiro E, Oldershaw PJ, Sacchetti R, Gibson DG. Non-invasive assessment of changes in left ventricular relaxation by combined phono-, echo-, and mechanocardiography. *Br Heart J* 1982;47:253–60.

20 Blaustein AS, Gaasch WH. Myocardial relaxation 6. Effects of beta-adrenergic tone and asynchrony on LV relaxation rate. *Am J Physiol (H)* 1983;**244**:417–22.

21 Frederiksen JW, Weiiss JL, Weisfeldt ML. Time constant of isovolumic pressure fall: determinants in the working left ventricle. *Am J Physiol (H)* 1978;**235**:701–6.

22 Eichhorn P, Grimm J, Koch R, Hess O, Carroll J, Krayenbuehl HP. Left ventricular relaxation in patients with left ventricular hypertrophy secondary to aortic valve disease. *Circulation* 1982;**65**:1395–404.

23 Eger EI II. Isoflurane: a review. *Anesthesiology* 1981;**55**:559–76.

24 Brutsaert DL, Housmans PR, Goethals MA. Dual control of relaxation. its role in the ventricular function in the mammalian heart. *Circ Res* 1974;**44**:637–52.

25 Zile MR, Gaasch WH, Wiegner AW, Robinson KG, Bing OHL Mechanical determinants of maximum isotonic lengthening rate in rat left ventricular myocardium. *Circ Res* 1987;**60**:815–23.

26 Katz LN. The role played by the relaxation in filling of the ventricle. *Am J Physiol* 1930;**95**:542–50.

27 Winegrad S, Weisberg A, McClennan G Are restoring forces important to relaxation? *Eur Heart J* 1980;**1**:suppl A.59–66

28 Sonnenblick EH. The structural basis and important of restoring forces and elastic recoil for the filling of the heart. *Eur Heart J* 1980;**1**:A-107–10.

29 Templeton GH, Wildenthal K, Willerson JT, Reardon WC. Influence of temperature on the mechanical properties of cardiac muscle. *Circ Res* 1974;**34**: 624–34.

30 Goldberg LI. Effects of hypothermia on contractility of the intact dog heart. *Am J Physiol* 1958.92–8.

31 Luke RA, Gillbe CE, Bonser RS, Paneth M, Gibson DG. Effect of temperature on the rate of left ventricular pressure fall in humans [Abstract]. *Circulation* 1987;**76**(suppl IV):512.

Br Heart J 1989;**61**:432–4

Balloon dilatation of stenosed Blalock-Taussig shunts

SHAKEEL A QURESHI,* ROBIN P MARTIN,* DAVID F DICKINSON,†
STEWART HUNTER‡

From the Departments of Paediatric Cardiology, Royal Liverpool Children's Hospital, Liverpool; †Killingbeck Hospital, Leeds; and ‡Freeman Hospital, Newcastle Upon Tyne*

SUMMARY Three patients with complex cyanotic congenital heart disease, who had previously undergone Blalock-Taussig shunt operations, developed severe stenoses at the pulmonary anastomosis of the shunts. All were successfully treated with balloon dilatation, which can thus be considered an effective alternative to reoperation.

When a Blalock-Taussig shunt becomes stenosed the therapeutic options include the creation of another systemic-pulmonary artery shunt or, if suitable, correction of the underlying cardiac malformation earlier than planned. Balloon angioplasty has been used for successful dilatation of a wide range of arterial stenoses and new applications continue to be reported. We report the successful dilatation of severely stenosed Blalock-Taussig shunts in three children with complex cyanotic congenital heart disease.

Patients and methods

Three children underwent percutaneous balloon dilatation of stenosed Blalock-Taussig shunts. The group consisted of a three year old boy with Down's syndrome, tetralogy of Fallot, and complete atrioventricular septal defect (patient 1); a nine year old girl with a common atrioventricular valve connection to a morphologically left ventricle and pulmonary atresia (patient 2); and a 12 year old boy with dextrocardia, situs solitus, atrioventricular concordance, a straddling right atrioventricular valve, ventricular septal defect, transposition of the great arteries, and pulmonary atresia (patient 3).

Patient 1 developed cyanotic spells at the age of two years three months and had a right Blalock-Taussig shunt operation. Seven months later he became more cyanosed and shunt angiography showed a discrete and severe stenosis at the anastomosis of the shunt (fig 1).

Patient 2 had a right Blalock-Taussig shunt operation when she was one year old. A year later, because of increasing cyanosis, a left Blalock-Taussig shunt was performed. At the age of eight years, she became more cyanosed. Angiocardiography and shunt angiography showed moderately severe atrioventricular valve regurgitation and severe stenosis at the anastomoses of both the shunts.

Patient 3 had a right Blalock-Taussig shunt at the age of one month. Five years later, a left modified Blalock-Taussig shunt with a 6 mm diameter

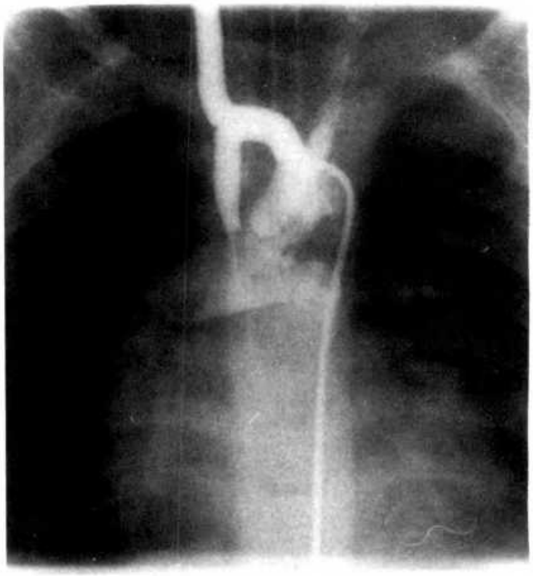


Fig 1 *Shunt angiogram in the anteroposterior projection showing a discrete stenosis at the shunt anastomosis to the right pulmonary artery in patient 1.*

Present address and requests for reprints to Dr Shakeel A Qureshi, Department of Paediatric Cardiology, Guy's Hospital, St Thomas Street, London SE1 9RT.

Accepted for publication 24 January 1989

polytetrafluoroethylene graft was performed because of increasing cyanosis. When he was 12 years old further cyanosis prompted shunt angiography, which showed severe stenosis of the anastomosis of the right shunt and a patent and unobstructed left modified shunt.

TECHNIQUE OF BALLOON DILATATION

Cardiac catheterisation was performed percutaneously by the femoral venous and arterial routes under general anaesthesia in all cases. A 6 French multipurpose catheter was passed from the femoral vein and placed in the right atrium for access. A 5 French multipurpose end hole catheter was then passed retrogradely through the femoral artery and placed at the origin of the Blalock-Taussig shunts. Shunt angiography was performed to confirm the site and the severity of the stenoses and to measure the diameter of the shunt. The external dimension of the catheter was measured on a still frame of the cineangiogram and the magnification factor was calculated by dividing this by the actual external diameter of the catheter. The diameter of the midportion of the subclavian artery shunt was then measured on a still frame and this value was divided by the magnification factor previously obtained to give the actual diameter of the shunt. We selected a balloon with an external diameter 1–2 mm greater than the shunt diameter.

A 175 cm long 0·020 inch (0·5 mm) diameter steerable exchange guide wire was then used to manipulate the end hole catheter across the stenosis into the distal pulmonary artery on the side of the shunt in patients 2 and 3 and into the pulmonary trunk and through the pulmonary valve into the right ventricle in patient 1. Heparin (50 units/kg) was given intravenously to each patient. The guide wire was kept in position as the catheter was exchanged for a Schneider Medintag balloon catheter of appropriate balloon diameter. In patients 1 and 3 a balloon catheter with an external diameter of 6 mm was used for dilatation, and in patient 2 a balloon with an external diameter of 8 mm was used to dilate the right shunt and one of a 10 mm diameter for the left shunt. The balloon was inflated two or three times at each site to a pressure of 404 kPa (4 atm) for 10–15 seconds and then deflated. The guide wire was kept in position as the balloon catheter was exchanged for the end hole catheter and shunt angiography was repeated.

Results

There were no complications during the procedure in the three patients. At the end of the procedure, the foot pulses were easily palpable. Repeat shunt angiography immediately after balloon dilatation showed successful relief of the stenoses (fig 2) in each patient. Good flow was demonstrated through the shunts into the pulmonary arteries.

During a follow up of 6–16 months all three children remained adequately palliated. They were pink and had loud shunt murmurs.

Discussion

Patients with complex cyanotic congenital heart disease may occasionally be unsuitable for surgical correction (as in patients 2 and 3), and therefore are considered for palliative surgery only. If, however, they are suitable for correction (patient 1), then it may be preferable to delay operation until the age of 5–10 years. Palliation, consisting of a systemic to pulmonary artery shunt, is then performed to help the patients attain the appropriate age and size for correction.

Early or late occlusion occurs in approximately 10% of Blalock-Taussig shunts,[1 2] but the incidence of discrete stenosis of the shunt anastomosis, which may be difficult to detect clinically, is unknown. If the shunt becomes occluded, a further shunt may be necessary, but the development of a discrete stenosis at the anastomotic site may be amenable to balloon dilatation.

Balloon angioplasty has been increasingly con-

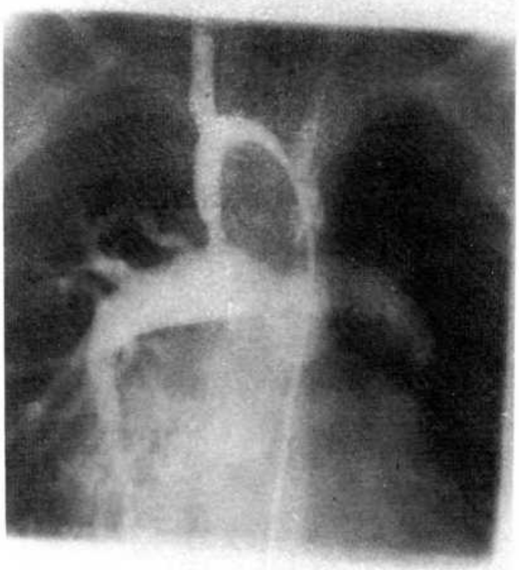


Fig 2 *Shunt angiogram in the anteroposterior projection after balloon dilatation, showing successful relief of the stenosis in patient 1.*

sidered as the standard procedure for treating recoarctation of the aorta after previous operation,[3-5] where the restenosis is thought to be caused by a dense fibrous tissue reaction. A Blalock-Taussig shunt may become stenosed by a similar tissue reaction at its anastomosis into the pulmonary artery. Therefore balloon dilatation may be a useful treatment for stenosed shunts. To date there has been only one report of successful balloon dilatation of a stenosed Blalock-Taussig shunt.[6]

In patient 1 flow into the pulmonary circulation occurred through the pulmonary valve and through the Blalock-Taussig shunt; in patients 2 and 3 it occurred only through the left and right shunts. Thus flow into the pulmonary circulation was maintained during balloon inflation and any haemodynamic disturbances were prevented. In patients with shunt-dependent pulmonary blood flow, shunt dilatation could be more hazardous—possibly resulting in hypoxia, metabolic acidosis, and arrhythmias. Rapid placement and inflation of the balloon catheter would be required.

Generally, an exchange wire of the diameter appropriate for the balloon catheter is used. However, the use of a steerable guide wire makes it technically easy and quick to cross the severe anastomotic stenoses. This facilitates the passage of the balloon catheter over the stiffer portion of the guide wire into the shunt. We used a balloon that when inflated had a diameter approximately 1–2 mm larger than that of the subclavian artery; this produced satisfactory results in all the patients with no early complications. Further follow up is necessary to determine whether late complications such as aneurysm formation or restenosis occur.

We believe that balloon dilatation of stenosed Blalock-Taussig shunts is a reasonable and safe alternative to reoperation in those patients who are unsuitable for surgical correction and in those in whom the correction needs to be delayed.

References

1 Arciniegas E, Farooki ZQ, Hakimi M, Perry BL, Green EW. Classic shunting operations for congenital cyanotic heart defects. *J Thorac Cardiovasc Surg* 1982; 84:88–96.

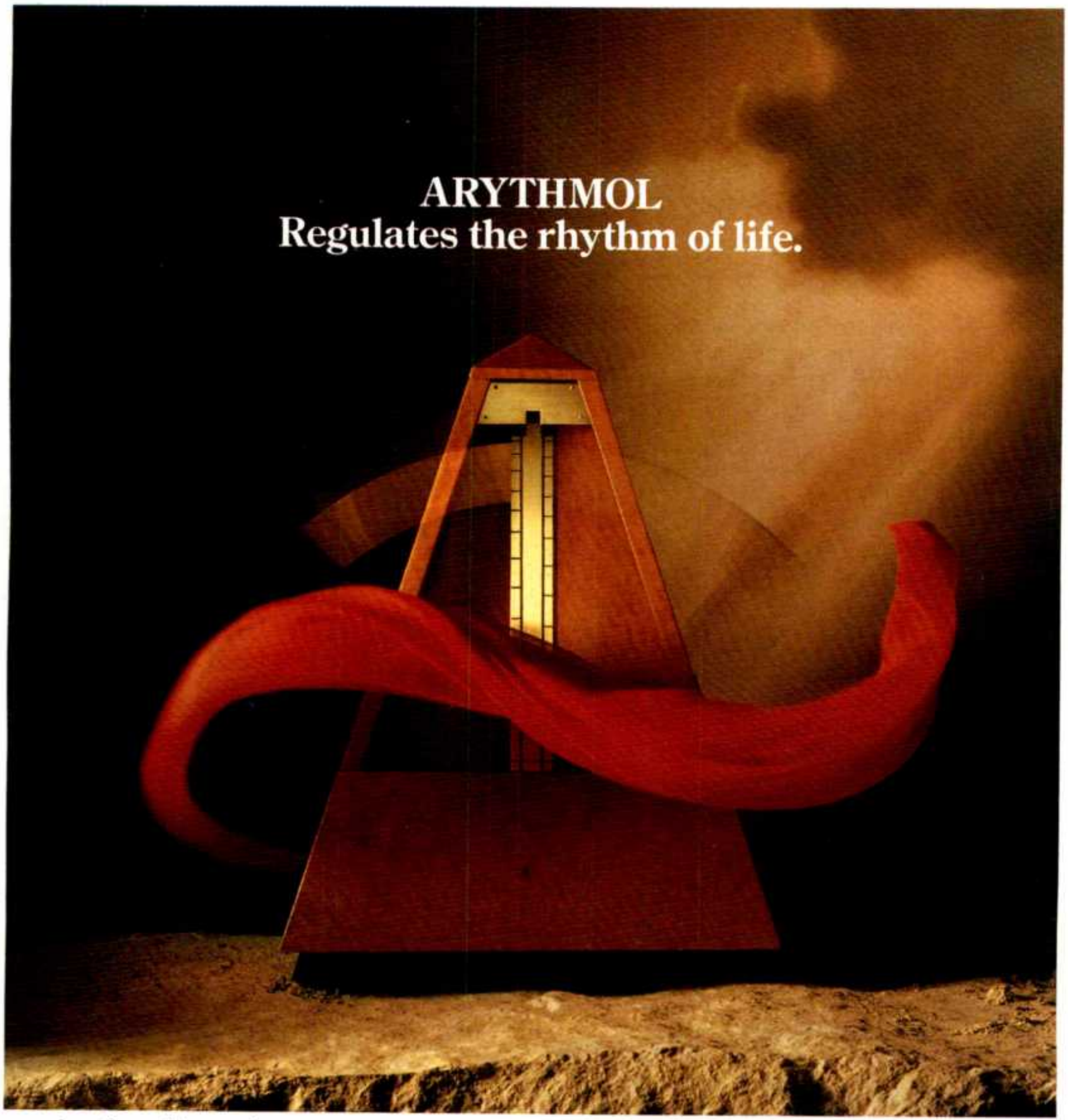
2 Stewart S, Alexson C, Manning J, Oakes D, Eberley SW. Long term palliation with the classical Blalock-Taussig shunt. *J Thorac Cardiovasc Surg* 1988; 96:117–21.

3 Lock JE. Catheter intervention. balloon angioplasty. In: Lock JE, Keane JF, Fellows KE, eds. *Diagnostic and interventional catheterization in congenital heart disease.* Boston: Martinus Nijhoff, 1987:91–110.

4 Kan JS, White RI Jr, Mitchell SE, Farmlett EJ, Donahoo EJ, Gardner TJ. Treatment of restenosis of coarctation by percutaneous transluminal angioplasty. *Circulation* 1983;68:1087–94.

5 Saul JP, Keane JF, Fellows KE, Lock JE. Balloon dilatation angioplasty of postoperative aortic coarctation [Abstract]. *J Am Coll Cardiol* 1986;7:117A.

6 Fischer DR, Park SC, Neches WH, *et al.* Successful dilatation of a stenotic Blalock-Taussig anastomosis by percutaneous transluminal balloon angioplasty. *Am J Cardiol* 1985;55:861–2.


ARYTHMOL
Regulates the rhythm of life.

Arythmol is an important antiarrhythmic agent, new to the United Kingdom. Its proven efficacy and favourable side effect profile[1] make Arythmol an important consideration when treating ventricular arrhythmias, even in selected patients with poor left ventricular function.[2]

References: 1 Singh BN et al. Am Heart J 1988; **116:** 1542-1550.
2 Baker BJ et al. J Electrophysiol 1987; **1:** 527-535.

ARYTHMOL
propafenone HCl

knoll
BASF Group

▼ **ABBREVIATED PRESCRIBING INFORMATION Presentation** White, film coated 150mg and 300mg tablets containing propafenone hydrochloride. **Indications** Prophylaxis and treatment of ventricular arrhythmias. **Dose** Individual maintenance dose should be determined under cardiological surveillance and hospital conditions. **Adults** Initially 150mg three times daily increasing at a minimum of 3 day intervals to 300mg twice daily and, if necessary, to a maximum of 300mg three times daily. **Elderly patients: patients with impaired hepatic or renal function** A reduction in the recommended dose is advisable. **Contraindications** Uncontrolled heart failure, cardiogenic shock (except arrhythmia induced), bradycardia, uncontrolled electrolyte disturbances, severe obstructive pulmonary disease, marked hypotension. Unless adequately paced, ARYTHMOL should not be used in the presence of sinus node dysfunction, atrial conduction defects, second degree or greater atrioventricular block, bundle branch or distal block. **Precautions** The minor negative inotropic effect of ARYTHMOL may assume importance in patients predisposed to heart failure. Effects of ARYTHMOL may be potentiated if given with other local anaesthetic type agents or agents which depress myocardial activity. Reduced doses of digoxin, warfarin, propranolol and metoprolol may be required when given in combination with ARYTHMOL. Plasma levels of ARYTHMOL may be increased by concomitant administration of cimetidine or quinidine. ARYTHMOL has been shown to decrease pacemaker sensitivity and increase pacing thresholds. ARYTHMOL should not be used during pregnancy. **Side effects** Generally well tolerated. Minor side effects at high doses usually relate to the nervous system and cardiovascular system. Dizziness, nausea, vomiting, fatigue, bitter taste, constipation, diarrhoea, headache, blurred vision, dry mouth may occur. More rarely, bradycardia, sinoatrial, atrioventricular or intraventricular conduction blocks and hypotension may occur. Small risks of proarrhythmic effects. Very rarely hypersensitivity reactions (e.g. skin rash, cholestasis, blood dyscrasias, lupus syndrome) and seizures may occur. All side effects are reversible on discontinuation of treatment. **Product licence numbers** ARYTHMOL tablets 150mg 0169/0015, ARYTHMOL tablets 300mg 0169/0016. **Basic NHS price** ARYTHMOL 150mg x 90 – £19.98, ARYTHMOL 300mg x 60 – £19.98. Further information available from Knoll Ltd, Fleming House, 71 King Street, Maidenhead, Berkshire SL6 1DU.

NATIONAL HEART & LUNG INSTITUTE
BROMPTON HOSPITAL

CARDIAC DOPPLER ULTRASOUND

27–29 SEPTEMBER 1989

A course on cardiac Doppler ultrasound for physicians, technicians and radiologists with a basic knowledge in echocardiography. A series of lectures, demonstrations and practical sessions will cover all aspects of cardiac Doppler ultrasound including colour Doppler flow mapping in adult and congenital heart disease.

Speakers will include

Professor R H Anderson
Dr D G Gibson
Dr A B Houston
Dr M L Rigby
Dr I A Simpson

Course fee: **£200.00** (to include coffee, lunch, tea and the course dinner)

The programme and application forms may be obtained from;

The Postgraduate Centre
National Heart & Lung Institute
Dovehouse Street
London SW3 6LY

Telephone enquiries. **01-351 8172** (direct line)

HAMAD MEDICAL CORPORATION
DOHA – QATAR – ARABIAN GULF

invites candidates for a Consultant position in

Pediatric Invasive Cardiology

REQUIREMENT

Board certification or equivalent and at least three years of experience.

BENEFITS

★ Attractive tax free salary
★ Furnished accommodation
★ 50 days annual leave
★ Annual air passage to home country
★ 3 years contract and renewable upon mutual agreement

HOW TO APPLY

Qualified applicants should send complete CV with contact telephone number and address to:

Medical Director
Hamad Medical Corporation
P.O. Box 3050
Doha – Qatar
Arabian Gulf

Br Heart J 1989;61:435–82

Proceedings of the British Cardiac Society

THE 68th ANNUAL GENERAL MEETING of the British Cardiac Society was held at the Academic Centre, the John Radcliffe Hospital, Oxford on Thursday and Friday, 6 and 7 April 1989.

The President, E Sowton, took the Chair during private business. D A Chamberlain was elected as President-Elect and Kim Fox, P Hubner, and M E Scott were elected to Council on the retirement of J Horgan, M Petch, and D Wheatley.

Deaths during the year: K Datey, P Duchosal, W Evans, J Pilcher, I McD Stewart.

New Members 1989: G Baines; G Bergman; C Bucknall; G Butrous; T Crake; J Dark; R Dawson; J Dhasmana; M Elliott; M Gammage; D Gladstone; W Hubbard; S Hutchison; N Irvine; P McSorley; R Martin; M Monaghan; D Murray; M Norell; I Peart; R Perry; S Pugh; E Rodrigues; B Sethia; J Skehan; D Sugrue; I Sullivan; G Venn; K Walsh; P Weissberg; J Wilson; J Wright.

New Corresponding Members: Avraamides (Cyprus); Bourdillon (USA); Eyjolfsson (Iceland); Hassell (Barbados); Nicolaides (Cyprus).

During the meeting the scientific sessions were held under the chairmanship of P Sleight and the following are abstracts of the papers that were presented.

Hypocapnia during exercise testing in dilated cardiomyopathy and hypertrophic cardiomyopathy: objective assessment by respiratory gas analysis

D P Moore, D Gilligan, C M Oakley
Department of Clinical Cardiology,
Hammersmith Hospital, London

End tidal carbon dioxide concentration (etCO_2) rises progressively during exercise in normal subjects, with a small decline at peak workload, although it remains above 35 mm Hg. Symptom limited bicycle ergometry was performed in 15 patients with dilated cardiomyopathy (group 1), 10 patients with hypertrophic cardiomyopathy (group 2), and 10 controls (group 3). Oxygen consumption (Vo_2), minute ventilation (VE), etCO_2, electrocardiogram, and blood pressure were monitored during the test. Resting etCO_2 was 34·7 (4·9) in group 1, 33·3 (2·6) in group 2, (NS), but 38·1·(2·3) mm Hg in group 3 ($p < 0·05$). Resting VE (l/min) was significantly higher in group 1 (14·6 (3·7)) than in group 2 (11·0 (1·2)), or group 3 (10·5 (2·2)) ($p < 0·02$). Exercise capacity (Vo_2 max ml/min/kg) was lower in group 1 (15·8 (4·3)) and group 2 (15·7 (4·8)) than in group 3(37 8 (6·0)) ($p < 0·001$). There was no significant difference between groups 1 and 2. Maximum exercise duration (seconds) was lower in both group 1 (453 (187)) and group 2 (485 (187)) than in group 3 (1377 (173)) ($p < 0·001$) but there was no significant difference between groups 1 and 2. Peak exercise etCO_2 fell in all groups, but in group 3 it remained within the normal range (36·6 (4·2) mm Hg). In group 1 etCO_2 fell to 31·4 (7·8) mm Hg ($p < 0$ 05 *v* group 3) and in group 2 to 30·8 (6·4) mm Hg, ($p < 0·01$ *v* group 3). Peak exercise blood pressure was lower in groups 1 and 2 than in group 3 (131 (32) and 136 (26) *v* 172 (26) mm Hg, $p < 0·05$). There was no significant correlation between exercise hypocapnia and maximum blood pressure. In four patients in group 2 with exercise provoked hypocapnia arterial blood gas samples confirmed a fall in arterial Pco_2 during exercise, which correlates closely with etCO_2, but there was no significant change in arterial pH.

Significant hypocapnia induced by hyperventilation may contribute to exercise limitation in cardiomyopathy. The occurrence of exertional hypocapnia may be a consequence of raised left atrial pressure or may reflect altered neural control of breathing.

Increased exercise capacity and reversal of exercise induced myocardial ischaemia in haemodialysis patients treated with recombinant human erythropoietin

N P Lewis, I C Macdougall, G A Coles,
J D Williams, K A A Fox
Department of Cardiology, University Hospital of Wales, Cardiff and Kidney Research Unit Fund, Institute of Renal Diseases, Cardiff Royal Infirmary, Cardiff

The importance of electrocardiographic evidence of exercise induced myocardial ischaemia in anaemic haemodialysis patients has not been defined nor is the influence of recombinant erythropoietin (rHu EPO) on the reversal of such ischaemia known. Accordingly, exercise performance, respiratory gas analysis, and electrocardiographic evidence of myocardial ischaemia were assessed in 10 patients on maintenance haemodialysis (six men, mean age 43, range 23–76 years) before and after eight weeks' intravenous rHu EPO (120 U/kg twice weekly). Maximal exercise testing was performed according to the Weber treadmill protocol and respiratory gases were analysed by mass spectrometry with the argon dilution method. Electrocardiographic evidence of myocardial ischaemia was defined as the presence of $\geq 0\cdot1$ mV horizontal or downsloping ST segment depression during exercise in the absence of bundle branch block. All the electrocardiograms were assessed blindly. After eight weeks' treatment with rHu EPO, the mean (SD) concentration of haemoglobin increased from 6·3 (0·6) to 10·2 (1·1) g/dl ($p<0\cdot001$). Exercise time increased from 13·2 (5·5) to 20·0 (6·2) minutes ($p<0\cdot001$); maximal oxygen consumption increased from 20·2 (7·0) to 25·9 (6·6) ml/min/kg ($p<0\cdot02$) and the anaerobic threshold from 12·7 (3·5) to 16·3 (3·8) ml/min/kg ($p<0\cdot001$). In seven patients ischaemic electrocardiographic changes were induced by exercise in the baseline study, and these were reversed in all but one patient after erythropoietin ($p<0\cdot01$).

We conclude that exercise capacity is impaired in anaemic haemodialysis patients by reduced tissue oxygen delivery and that exercise capacity is improved by modest changes in haemoglobin. Impaired myocardial oxygen supply is frequently found on exercise, and exercise induced myocardial ischaemia is readily reversed by modest increases in haemoglobin after treatment with recombinant erythropoietin.

Critical level of exercise capacity determines the hyperventilation response to exercise in chronic heart failure

S W Davies, T M Emery, M I L Watling,
D P Lipkin
The Royal Free Hospital, London

Patients with chronic heart failure (CHF) who are limited by dyspnoea ventilate more than do normal subjects at the same workload; the ratio of minute ventilation to minute production of carbon dioxide (VE/Vco_2) is increased in CHF and this may reflect pulmonary ventilation-perfusion mismatch. The respiratory response to progressive treadmill or bicycle exercise was studied in 40 patients with CHF (New York Heart Association grade II-III) and in 289 normal subjects with no evidence of cardiac or pulmonary disease. Exercise capacity was assessed by the peak oxygen consumption (Vo_2max) achieved during progressive exercise, and end tidal carbon dioxide, respiratory rate (RR), and the ratio VE/Vco_2 were measured. In the CHF patients, Vo_2max ranged from 10 to 22 ml/kg/min (mean 16); VE/Vco_2 was 22·7 (4·8) and correlated strongly with Vo_2max ($R = -0\cdot5$, $p < 0\cdot002$). End tidal carbon dioxide at peak exertion was 5·8 (0·5)% and peak RR was 30 (2) per minute. In normal subjects Vo_2max ranged from 30 to 83 ml/kg/min (mean 42); VE/Vco_2 was 25·8 (3·2) and did not correlate with Vo_2max. End tidal carbon dioxide at peak exertion was 5·4 (0·7)% and peak RR was 32 (6) per minute.

End tidal carbon dioxide and RR on exercise are similar in normal subjects and in CHF; thus the increased VE/Vco_2 suggests a ventilation-perfusion mismatch. While in moderate to severe CHF VE/Vco_2 is correlated with Vo_2max, there is no such relation across the group of normal subjects, suggesting a threshold of Vo_2max below which VE/Vco_2 is affected. This would be explained if there is a critical level of cardiac function that is necessary to perfuse adequately all the lung zones on exercise and so avoid the ventilation-perfusion mismatch.

Functional and angiographic comparison of symptomatic and silent ischaemia

J P Fox, J M Beattie, M S Salih, M K Davies,
W A Littler, R G Murray
University Department of Cardiovascular Medicine, East Birmingham Hospital, Birmingham

Silent ischaemia is increasingly diagnosed in people with clinical or occult coronary heart disease (CAD). Although this finding may carry implications for prognosis and possible therapeutic intervention, the underlying pathophysiology remains ill defined. We compared the frequency of occlusive CAD at angiography in 103 patients with exercise induced painful or silent ischaemia after acute myocardial infarction. After rehabilitation, all patients showed ≥ 1 mm ST segment depression in infarct remote leads during submaximal treadmill exercise and 52 remained symptom free. Angiographic assessment (< 3 months) of the extent and severity of CAD was facilitated by Gensini scoring (GS), incorporating a weighting factor proportionate to the potential total ischaemic burden. Ischaemic thresholds were compared as total exercise time (ET) and double product (DP) (mean (SD)). Despite similar resting ejection fractions of 54 (16) and 54 (14)% and peak haemodynamic loads manifest by DP of 16·2 (3·7) and 17·4 (4·2 (× 10^3) for the painful and silent groups respectively (NS), ET was longer in those with silent ischaemia (11·4 (5) min) than in those with painful ischaemia (8·7 (5) min) ($p < 0·01$). GS was similar in those with painful ischaemia (55 (16) and 45 (29) in those with silent ischaemia. Collateral vessels were identified in 49% of those with painful ischaemia and 50% of those with silent ischaemia and did not seem to mediate this disparate symptomatic response.

Similar CAD profiles were evident in both clinical groups and such "silent" changes should therefore be accorded equal importance when post-infarct patients are screened for residual CAD.

Inefficient gait contributes to reduced exercise capacity in chronic heart failure

S W Davies, C Greig, S L Jordan, D W Grieve, D P Lipkin
The Royal Free Hospital, London

The metabolic cost of walking is affected by stride length. The present study evaluated whether the walking pattern is altered in chronic heart failure (CHF) so as to affect the oxygen cost of exercise. The stride length was recorded in eight patients with severe CHF (New York Heart Association grade III), in 10 with mild/moderate CHF (grade II), and in 10 age matched healthy controls during both free walking and treadmill exercise. Stride length was normalised for height by calculation of the relative stride length (RSL). The RSL was shorter in severe CHF (0·47 (0·10) (mean (SD))) than in mild/moderate CHF (0·64 (0·05)) ($p < 0·05$) and healthy controls (0·66 (0·05)) ($p < 0·02$). Exercise capacity was assessed in CHF patients by peak oxygen consumption ($\dot{V}O_2max$) during symptom limited progressive treadmill exercise. RSL was correlated with $\dot{V}O_2max$ ($R = +0·5$, $p < 0·05$). To compare the oxygen cost of short stride with that of a normal gait, control subjects performed submaximal treadmill exercise (2 mph, level) to steady state, both when walking normally and again when stepping in time to a metronome adjusted to give an RSL as short as that in severe CHF. A short RSL led to a 16% increase in steady state $\dot{V}O_2$ from 11 (1) to 13 (1) ml/kg/min ($p < 0·05$).

Patients with severe CHF have a short-stepping gait. A short-stepping gait carries a higher oxygen cost for the same external workload, and this reduced efficiency will contribute to the limitation of exercise capacity in these patients.

The perception of angina in diabetic patients: evidence of silent exertional ischaemia

G Ambepitiya, P G Kopelman, D Ingram, R MacDonald, P G Mills, A D Timmis
Newham General, London Chest, and London Hospitals

Diabetic patients are more liable to silent myocardial infarction but it is not known whether their perception of angina is also impaired. We measured perception of angina as the time from onset of ST depression to onset of angina during treadmill exercise (Bruce protocol) in 32 diabetic patients (group A) and 36 non-diabetic controls (group B) all with exertional angina and ST depression. There were no significant age or sex differences between the groups and both achieved similar peak heart rates (125 (22) *v* 128 (20) beats/min) and blood pressure responses (164 (27) *v* 154 (26) mm Hg). Ischaemia at peak exercise was similar in both groups ($\sum$ST depression 0·6 (0·3) *v* 0·7 (0·4) mV) but ST depression occurred earlier in group A (111 (82) *v* 216 (162) s; $p < 0·002$). Moreover, the time from onset of ST depression to onset of angina was considerably longer in group A than in group B (149 (76) *v* 63 (59) s; $p < 0·001$), indicating that the perception of angina after the onset of electrical ischaemia was impaired in the diabetic patients. Autonomic function tests showed that the time to onset of angina correlated negatively with the heart rate responses to deep breathing ($r = 0·3$, $p < 0·02$) and the Valsalva manoeuvre ($r = 0·4$, $p < 0·001$). Electromyographic studies of the median nerve showed normal motor function in group A but impaired sensory function as reflected by increased latency (3 2 (0·6) *v* 2·5 (0·4) ms; $p < 0·01$) and reduced conduction velocity (45 (8) *v* 55 (5) m/s; $p < 0·001$).

In diabetic patients the perception of angina is impaired in association with autonomic and sensory neuropathy. At low levels of exertion ischaemia may remain entirely silent and predispose diabetic patients to the later development of specific heart muscle disease.

Emergency coronary bypass surgery after vessel occlusion at angioplasty in centres without on-site facilities for cardiac surgery

T R D Shaw, I R Starkey, A R Essop, R Sutton, M K Davies, R G Murray, W A Littler
Western General Hospital, Edinburgh; Westminster Hospital, London; and East Birmingham Hospital, Birmingham

Three hundred and eighty nine coronary angioplasties were carried out at three cardiac laboratories in the United Kingdom without on-site cardiac surgery. Distances from the associated surgical units were three, two, and 22 miles. Total angioplasties at the invididual centres were 268, 71, and 50. Twelve patients (3·1%) required emergency coronary bypass surgery: 11 had stable angina and one had unstable angina. The vessel occluded was the anterior descending in five, circumflex in three, and right coronary artery in three—one patient, having circumflex dilatation, developed main stem dissection. Occlusion developed during the procedure in 11 patients while one had late occlusion. Between occulsion and surgery four patients were given DC shock for ventricular arrhythmia, all successfully. One patient required inotrope treatment during transfer. The interval between occlusion and operation was 45–120 minutes. The mean number of grafts was two. All 12 patients had good left ventricular function before angioplasty. Five developed Q wave changes and two developed new non-Q changes on the electrocardiogram. After operation left ventricular function was good in eight, moderate in three, and poor in one. The patient with main stem stenosis developed poor left ventricular function and died one month later—an angioplasy procedure mortality of 0·3% and a surgical mortality of 8%. Of the other 11 patients, nine were in New York Heart Association symptom class I and two in class II at three months after operation.

Coronary angioplasty can be performed with acceptable safety without on-site facilities for cardiac surgery if cases are selected appropriately, angioplasty timed carefully, and transit to the surgical unit is rapid.

Early clinical experience with a laser wire for percutaneous angioplasty of chronically occluded coronary arteries

R J Bowes, G D G Oakley, J S Fleming, D C Cumberland
Regional Cardiac Centre, Northern General Hospital, Sheffield

The role of percutaneous coronary angioplasty is considerably limited by low primary success in chronic occlusions. The laser wire is a new device consisting of a fibreoptic laser energy delivery system contained within a 0 018 inch diameter steerable guide wire which can be introduced through conventional balloon catheters. The distal metal tip allows delivery of the laser energy by direct thermal contact. A continuous wave argon laser generator is used at a power of 3 to 4 W. We used the device in seven men with stable angina pectoris. All had an angiographically documented coronary artery occlusion not associated with acute ischaemia: four of the right coronary artery (RCA) and three of the left anterior descending artery (LAD). Intervals between diagnostic angiography and the angioplasty procedures varied from six weeks to six months. One RCA occlusion and two LAD occlusions were successfully traversed by the wire, with subsequent successful balloon dilatation. There were no complications in either failed or successful procedures.

Our initial experience with the laser wire shows promise in improving the results of angioplasty in chronic coronary artery occlusions.

Long term clinical results after successful coronary angioplasty in multivessel disease

R A Henderson, Sheila Karani, C Bucknall, E Sowton
Guy's Hospital, London

In selected patients with multivessel coronary disease, angioplasty may offer a therapeutic alternative to coronary bypass surgery. The short term results of angioplasty have been established, but the long term results in patients with multivessel disease have not been clearly defined. We therefore analysed the late clinical outcome in 270 patients with multivessel disease who underwent successful coronary angioplasty of at least one coronary lesion. Before angioplasty, myocardial infarction had occurred in 51% and coronary bypass surgery had been performed in 18%. Most (73%) complained of severe (grade 3 or 4) angina. During follow up to four years over 60% remained free from angina and over 70% improved by two angina grades. Cumulative cardiac event rates were calculated, and at one year angioplasty had been repeated in 20% and coronary surgery had been performed in 14%. After four years 28% had required repeat dilatation, and 18% had undergone coronary surgery. Cardiac survival at four years was 87%, and the cumulative four year non-fatal myocardial infarction rate was 6%. Event free survival including freedom from cardiac death, myocardial infarction, and coronary surgery was 67% at four years.

In this series 70% of patients with multivessel disease were symptomatically improved in the long term. The frequent need for repeat revascularisation procedures emphasises the need for controlled clinical trials to assess the correct role of coronary angioplasty in the management of multivessel coronary disease.

Dilatation variables: the paradox of optimal improvement in stenosis by percutaneous transluminal coronary angioplasty and restenosis

K J Beatt, H E Luijten, H Suryapranata,
P J de Feyter, P W Serruys
Thoraxcenter, Erasmus University, Rotterdam,
The Netherlands

Detailed quantitative coronary angiography was performed on 490 successfully dilated lesions before percutaneous transluminal coronary angioplasty (PTCA), after PTCA, and at a mean follow up of 93 (45) days after dilatation. The absolute diameter of the stenosis (MLD) in mm, the normal diameter or the reference diameter of the dilated coronary artery segment (RD), and the percentage diameter stenosis (DS) were measured by a quantitative measuring system (CAAS) and the changes occurring in these variables at PTCA were calculated. Restenosis defined as a $\geqslant 0{\cdot}72$ mm deterioration in the vessel lumen (a criterion based on the 95% confidence intervals for determining a significant change) and the relative risk (RR) of fulfilling this criterion were assessed. At angioplasty the mean change in the minimum luminal diameter was 0·93 mm and the percentage diameter stenosis −29·0% and the changes from PTCA to follow up were −0·22 mm and 5·1% respectively. Forty three per cent of lesions fulfilling the $\geqslant 0{\cdot}72$ mm criterion had a DS of $\geqslant 50\%$. The risk of restenosis was not dependent on pre-PTCA morphology, the relative risk of restenosis being less than 1·5 for more severe lesions (MLD < 1 mm, DS $> 65\%$) and for larger vessels (RD > 3 mm). Post-PTCA lesions with the best angiographic results (MLD $> 2{\cdot}5$ mm, and DS $< 25\%$) had an increased risk of restenosis (RR $> 2{\cdot}0$, $p < 0{\cdot}001$). The single factor most predictive of restenosis was a large improvement in the vessel lumen (MLD improvement of $> 1{\cdot}14$ mm) with a RR for restenosis of 2·65 (95% confidence interval 1·81 to 3·89, $p < 0{\cdot}001$). If the restenosis criterion is chosen to reflect only the deterioration in lumen diameter from post-PTCA to follow up, then the greater the improvement at PTCA the greater the risk of restenosis. This is a stronger predictor of restenosis than the vessel size or the severity of the lesion before or after angioplasty.

Myocardial protection with diltiazem during coronary angioplasty: cardioplegic or vasodilatory action?

A Seth, R A Perry, S Smith, F F Shiu
Queen Elizabeth Hospital, Birmingham and
University of Birmingham

Diltiazem is a coronary vasodilator with cardioprotective potential. In a two-part study, intracoronary diltiazem was first given to 10 patients after diagnostic angiography in doses of 0·02, 0·04, 0·16, and 0·32 mg/kg. Great cardiac vein flow (by thermodilution), myocardial oxygen consumption, and left ventricular max dP/dt were measured at 1, 3, 5, and 10 minutes after each dose. Regional wall motion was assessed by a computerised technique of coronary artery shortening. The lowest dose (0·02 mg/kg) significanly increased in great cardiac vein flow (82 (34) *v* 139 (74) ml/min, $p < 0{\cdot}05$) and reduced regional wall motion 20 (6)% *v* 16 (7)%, $p < 0{\cdot}05$). Higher doses reduced left ventricular max dP/dt and blood pressure but did not further increase great cardiac vein flow. Five patients developed transient atrioventricular block at 0·04 mg/kg or above. In 12 patients undergoing percutaneous transluminal angioplasty of the left anterior descending coronary artery 0·02 mg/kg intracoronary diltiazem or placebo was given in random order before two successive balloon occlusions lasting a minute. Balloon occlusion resulted in a fall in great cardiac vein flow (111 (50) *v* 83 (46) ml/min, $p < 0{\cdot}05$) and myocardial oxygen consumption (9·6 (5·8) *v* 7·4 (3·6), $p < 0{\cdot}05$), and a rise in lactate concentration in the great cardiac vein (1075 (536) *v* 1175 (584), $p < 0{\cdot}05$). Administration of diltiazem abolished these changes: great cardiac vein flow (106 (72) *v* 108 (74)) ml/min, myocardial oxygen consumption (9·8 (5·3) *v* 9·1 (5·8)), great coronary vein *v* lactate (1078 (516) *v* 1136 (526)).

The study confirmed the cardioprotective action of diltiazem, which appears to be predominantly through maintenance of coronary blood flow—presumably via collateral channels.

Complication rates of single and multiple vessel coronary angioplasty in multivessel coronary artery disease

A C Hunt, J Escanade, S Chow, J Beattie, M F Shiu
Department of Cardiology, University of Birmingham, Birmingham

Multivessel coronary angioplasty (MVPTCA) has a higher procedural complication rate and mortality than single vessel coronary angioplasty (SVPTCA). This study over three consecutive years examined the effect of the presence or absence of coronary artery disease distant from the target angioplasty vessel. Data were obtained from 447 elective angioplasties. Patients were divided into three groups: in group 1—320 patients had SVPTCA in single vessel disease; in group 2 71 had SVPTCA in multivessel disease; and in group 3 56 had MVPTCA. The minor complications were prolonged pain, acute occlusions, and extensive dissections without myocardial infarction. Major complications were defined as myocardial infarction, death, or coronary artery bypass surgery. The complication rates in groups 1 to 3 were 14%, 17%, and 32% respectively and the major complication rates were 1·9%, 4%, and 7% respectively. The major complications included four deaths, six myocardial infarctions, and three bypass operations. Three of the deaths occurred during MVPTCA. Myocardial infarction (5) and CABS (3) accounted by most of the major complications in SVPTCA patients.

There was no significant difference in complication rates in patients with single vessel or multivessel disease undergoing SVPTCA. There was a significant increase in complication rates in patients undergoing MVPTCA as compared with SVPTCA (p < 0·001). Major complications, particularly death, were most common in MVPTCA (p < 0·001), less common in SVPTCA in multivessel disease, and least common in SVPTCA in single vessel disease.

Inositol phosphate production and proto-oncogene expression in left ventricle after the induction of coarctation hypertension in the rat

A M Heagerty, N K Green,* D H Maciver,
J A Franklyn,* M D Gammage*
Department of Medicine, University of Leicester and *Birmingham

The development of left ventricular hypertrophy is a serious consequence of hypertension and is associated with an increase in sudden death. The exact cellular processes that are implicated in generating the increased muscle mass are unclear, although recently there has been much interest in the phosphoinositide transmembrane signalling system and the expression of several proto-oncogenes during cell growth. This prompted the investigation of inositol 1,4,5 trisphosphate (Ins 1,4,5 IP$_3$) production and the expression of several proto-oncogenes considered important to growth in slices of left ventricle 72 hours after the induction of aortic coarctation in Wistar rats. Animals were killed and Ins 1,4,5 IP$_3$ was measured by high performance liquid chromatography and the m-RNA expression of the proto-oncogenes H-*ras*, c-*fos*, and c-*myc* investigated by dot hybridisation to specific radiolabelled cDNA probes. At 72 hours, carotid pressure was significantly higher in rats with coarctation than in sham operated animals (145 (+8) *v* 122 (5) mm Hg, p < 0·05). The concentration of Ins 1,4,5 IP$_3$ in the left ventricle (fmol/mg) was significantly raised in rats with coarctation (165 (29) (n = 10) *v* 93 (14·4) (n = 11), p = 0·004). Expression of H-*ras*, c-*fos*, and c-*myc* (DU/μgRNA) was increased in rats with coarctation (H-*ras*—1474 (224) *v* 628 (172), p < 0·001; c-*fos*—29·7 (5·4) *v* 10·2 (1·3), p < 0·01; c-*myc*—1300 (147) *v* 957 (176), p < 0·05).

These data suggest that the imposition of high pressure on the left ventricle induces enhanced expression of proto-oncogenes (whose products have been shown to be necessary for cell growth) and increased production of Ins 1,4,5 IP$_3$. It is concluded that these processes are related to the genesis of ventricular hypertrophy in this model of hypertension.

Autoradiographic localisation of [125$_{\text{I}}$] endothelin binding sites in human coronary artery: changes in ischaemic heart disease

M R Dashwood, A H Chester, R M Sykes,*
M H Yacoub
Harefield Hospital, Middlesex and *Royal Free Hospital School of Medicine, London

Endothelin is a 21 residue peptide with powerful vasoconstrictor activity in many blood vessels. The density and distribution of [125$_{\text{I}}$] endothelin binding sites in normal coronary arteries from five patients with cardiomyopathy were compared with the results in tissue from six patients with ischaemic heart disease. Tissue was frozen, cut in a cryostat at −20°C, and thaw-mounted on to gelatinised microscope slides. Sections were then incubated in 50 pmol/l [125$_{\mathrm{I}}$] endothelin (specific activity 1060 Ci/mmol, Peninsula Laboratories) for 60 minutes at 20°C and the degree of binding to nonspecific sites established by incubating in the presence of 500 nmol/l unlabelled endothelin. After incubation, sections were exposed to Hyperfilm ^{3}H (Amersham) or dipped in nuclear emulsion (Ilford) for autoradiography and processed after 12–21 days. There was a high specific binding of [125$_{\mathrm{I}}$] endothelin to coronary arteries. High resolution autoradiography (those dipped in nuclear emulsion) showed a high density of binding sites associated with the outer tunica media and perivascular nerves. There was no binding to endothelial cells. There was a considerable increase in binding [125$_{\mathrm{I}}$] endothelin in coronary arteries from patients with ischaemic heart disease, particularly in areas of the tunica media associated with an atherosclerotic plaque.

The presence of specific binding sites for [125$_{\mathrm{I}}$] endothelin, described here, suggests that endothelin may be an endogenous constrictor agent. The increased density of binding sites in atherosclerotic tissue may lead to increased constrictor effects of endogenous endothelin and contribute to the pathogenesis of ischaemic heart disease.

Myocardial proto-oncogene expression and effects of thyroid state

M D Gammage, J A Franklyn, N K Green,
M C Sheppard
Departments of Cardiovascular Medicine and
Medicine, University of Birmingham, Birmingham

The effects of thyroid hormones on myocardial cell growth are well documented; the mechanisms determining these . growth modulating effects are unknown. Because a fundamental role of specific proto-oncogene products in mediating growth signal transduction is suggested we examined the effect of thyroid state on expression of the c-*myc*, c-*fos*, and H-*ras* proto-oncogenes in the myocardium. Hypothyroid rats (treated with iodine-131 and propylthiouracil) were given triiodothyromine (2 or 20 µg subcutaneously daily); myocardial RNA was prepared by phenol chloroform extraction 6 or 72 h later and c-*myc*, c-*fos*, and H-*ras* mRNAs were determined by dot hybridisation to specific cDNA probes. Hypothyroidism was associated with an increase in c-*myc* mRNA, reversed by triiodothyramine (T3) at 72 h (control 10·8 (1·8) OD units/ µg RNA, hypothyroid 20·4 (2·7),* T3 2 µg 6 h 13·6 (1·8), T3 20 µg 6 h 16·4 (2·1), T3 2 µg 72 h 8·2 (1·6),† T3 20 µg 72 h 7·7 (1·8)‡ (*p < 0·05 compared with control, †p < 0·05, ‡p < 0·01 compared with hypothyroid, n = 8–10 in each group). In contrast, hypothyroidism and T3 treatment had no effect on c-*fos* mRNA (control 14·0 (2·3), hypothyroid 18·4 (4·2), T3 20 µg 6 h 12·6 (3·4), T3 20 µg 72 h 13·7 (3·5). There was an appreciable increase in H-*ras* mRNA in hypothyroid rats that was reversed by T3 at 72 h (control 1·3 (0·44), hypothyroid 16·9 (2·9)*, T3 2 µg 6 h 11·0 (1·5), T3 20 µg 6 h 15·1 (2·5), T3 2 µg 72 h 4·1 (0·25), †T3 20 µg 72 h 5·6 (2·3),† (*p < 0·001 compared with control †p < 0·01 ‡p < 0·05, compared with hypothyroid rats, n = 5).

These changes in c-*myc* and H-*ras* mRNA with thyroid state may determine the growth regulating effect of T3. Effects on both the nuclear transcription factor encoded by c-*myc* and the H-*ras* gene product, which are implicated in mediating membrane receptor signals, suggest complex influences of T3 on the myocardial cell membrane and nucleus in regulating cell growth.

Is the negative inotropy of angiotensin converting enzyme inhibitors the result of prevention of angiotensin II activity in human atrial muscle?

J M Walker, J Y Liu
University College and Middlesex Hospitals,
London

The relevance of tissue angiotensin converting enzyme (ACE) and local angiotensin II (AII) in heart muscle is unclear. ACE inhibitor drugs have effects on tissues other than the peripheral vessels; their negative inotropic action on the myocardium in vitro could be the result of interference with local AII production. The effect on the function of human atrial muscle of AII, its antagonist saralasin, and the ACE inhibitors captopril and lisinopril are reported. Specimens were obtained from patients undergoing coronary bypass grafting. Strips of muscle (< 1·0 mm diameter) were mounted to contract isometrically in an isolated organ bath superfused by Tyrode's solution at 37°C. Most required pacing (at 60 beats/min), although five experiments were carried out with spontaneously active muscles. We confirmed our previous observations that ACE inhibition had a modest negative inotropic effect (10% fall in tension with 1·0 μg/ml captopril or 100 ng/ml lisinopril). In spontaneously active muscles a reduction in beating was noted with ACE inhibition. Human sequence angiotensin II in approximately physiological doses from 0·1 ng/ml to 6·4 ng/ml produced a dose related increase in tension from 5% to 35% above control levels in all the muscles. A plateau in the positive inotropic effect of AII was noted; the dose at which this occurred varied between 0·32 ng/ml and 3·2 ng/ml. Angiotensin II produced an increase (+ 40%) in the rate of the spontaneous rhythm and caused spontaneous beating in one muscle, which had previously required pacing. The AII antagonist saralasin inhibited the positive inotropic effect of AII, but alone produced a 14% reduction in tension and a 15% reduction in the rate beating of one muscle.

These results imply that local generation of AII in the human atrium may affect mechanical and electrophysiological activity. Interference with locally generated AII in the heart may be one mechanism by which the ACE inhibitors influence heart function.

Beneficial effect of adenosine during reperfusion after prolonged cardioplegic arrest

S J M Ledingham, M Yacoub
National Heart and Lung Institute, London

Adenosine is a potent coronary vasodilator, a precursor of adenosine triphosphate, and may have protective effects on endothelial cells. We have investigated the influence of adding adenosine during reperfusion after cardioplegic arrest in the isolated working rat heart model. After three hours of hypothermic ischaemic arrest with St Thomas' Hospital Cardioplegic Solution No 1 (as used in clinical practice in the UK), hearts were reperfused with either ordinary perfusion fluid (Krebs-Henseleit bicarbonate buffer) or with additional adenosine (1 mg/l) for fifteen minutes before recovery of function was assessed. Ten hearts were used in each group. Mean coronary flow during reperfusion was 11·8 ml/min with ordinary perfusate and 17·6 ml/min with adenosine (p < 0·001). Mean recovery cardiac output (expressed as a percentage of its pre-ischaemic control) was 31·5% with ordinary perfusate and 64·5% with adenosine (p < 0·001).

Thus hearts that received adenosine had 50% greater coronary flow during reperfusion and 100% better recovery of cardiac function than hearts that did not. These observations suggest that adenosine may be useful in clinical practice, particularly after extended periods of cardioplegic arrest in transplantation.

Effects of sotalol on the rate of accumulation of extracellular potassium in ischaemic myocardium

M Hicks, S M Cobbe
Department of Medical Cardiology, Royal Infirmary, Glasgow

Previous studies of the effects of sotalol in ischaemic myocardium have shown a loss of the class III effect on action potential duration (APD) but indirect evidence suggesting a slowing of the rate of rise of extracellular potassium concentration $(K^+)_e$. We measured $(K^+)_e$ using ion-selective electrodes in the isolated arterially perfused interventricular septum of the rabbit heart before and during 30 min zero flow ischaemia. Intracellular action potentials were recorded by "floating" glass microelectrodes. Six septa were exposed to sotalol 10^{-4} mol before ischaemia, with six controls. Before ischaemia, sotalol caused an increase of APD$_{90}$ to 325 (16) ms compared with 261 (10) ms in controls. APD$_{90}$ shortened in both groups during ischaemia, with the effect of sotalol being lost after 6 min. Resting membrane potential fell from −75 (1) to −59 (2) mV after 30 min ischaemia in controls, while there was less depolarisation (−68 (2) mV, p < 0·001) after 30 min in the sotalol group. $(K^+)_e$ rose from 4·1 (0·2) to 13·1 (0·8) mmol after 30 min ischaemia but the rise was significantly attenuated from (3·9 (0·1) to 9·1 (1·0) mmol in the sotalol group (p < 0 005).

Sotalol reduced the rate of rise of $(K^+)_e$ and lessened depolarisation in ischaemic myocardium. These effects are potentially antiarrhythmic despite the loss of the class III effect.

Effects of cardiac hypertrophy on cellular electrophysiology during normal and ischaemic perfusion

S J Winterton, P Thomas, M A Turner, D J Sheridan
Department of Cardiology, St Mary's Hospital Medical School, London

Cardiac hypertrophy is associated with an increased risk of sudden death. To investigate the cellular electrophysiological (CEP) effects of hypertrophy we studied isolated hypertrophied guinea pig hearts, produced by aortic constriction (group I, $n = 11$, wet heart weight 4·7 (0·2) g) and sham-operated hearts (group II, $n = 11$, wet heart weight 3·5 (0·2) g, $p < 0{\cdot}005$) 30–50 days postoperatively. Hearts were rapidly removed and perfused with oxygenated Krebs solution at 32°C and paced at 3·3 Hz. Perfusion pressures were similar after 20 min control perfusion at 7 ml/min (group I 27 (1·7) mm Hg *v* group II 29 (2·0) mm Hg). Ventricular tachycardia or fibrillation occurred in both groups during ischaemia (flow reduced to 10% for 30 min: group I 88%, group II 66%) and reperfusion (flow returned to control value for 15 min: group I 88%, group II 66%). Control CEP recordings from the apex of the right ventricle by the floating microelectrode technique were similar in both groups and accorded with previous studies. During ischaemia hypertrophied hearts had a significantly lower Vmax (after 5 min group I 64 (3·8) V/s *v* group II 103 (9·5) V/s ($p < 0{\cdot}01$) and after 10 min group I 89 (14) V/s *v* group II 120 (7) V/s ($p < 0{\cdot}01$), APD_{50} at 2 min (group I 128 (2·9) ms *v* group II 139 (1·9) ms, $p < 0{\cdot}01$), and APD_{100} at 20 min (group I 107 (2·1) ms *v* group II 122 (3·1) ms, $p < 0{\cdot}01$) while the effective refractory period showed less initial prolongation and then greater shortening at 5 min (group I 129 (6·5) ms *v* group II 155 (5·7) ms, $p < 0{\cdot}01$) and at 10 min (group I 113 (3·5) ms *v* group II 135 (5·0) ms, $p < 0{\cdot}01$). Both groups recovered to normal on reperfusion.

These results suggest that the electrophysiological disturbances associated with myocardial ischaemia are increased in cardiac hypertrophy.

Long term prognosis and variability of myocardial ischaemia in syndrome X

G Pupita, J C Kaski, A R Galassi, F Crea,
A Maseri
Cardiovascular Unit, Hammersmith Hospital,
London

To evaluate the long term course of myocardial ischaemia in patients with syndrome X (typical angina pectoris, positive exercise test, no evidence of coronary spasm or left ventricular hypertrophy and angiographically normal coronary arteries), we studied 13 patients (10 women and three men, mean age 49 (7) years). Clinical and electrocardiographic variables as well as exercise test and Holter monitoring were assessed both when the diagnosis was first established (A) and after a mean follow up (F) of 6·3 years (range 3–9). Mean number of anginal episodes and weekly consumption of glyceryl trinitrate were similar at A and F and only two of the patients had pain free periods of at least one month. Exercise time, heart rate, and rate-pressure product at 1 mm of ST depression at A and F were similar: 594 (178) *v* 631 (202) s, 134 (20) *v* 139 (17) beats/min, 203 (52) *v* 216 (61) respectively ($p =$ NS for all). Twenty four hour Holter monitoring at A and F showed similar numbers of episodes of ST depression $\geq 0{\cdot}1$ mV (31 *v* 25), proportion of painful episodes (39 *v* 36%), and of episodes preceded by an increase in heart rate (39 *v* 32%). None of the patients developed serious coronary events, left ventricular failure, or bundle branch block during follow up.

Thus although syndrome X seems to have a benign prognosis, angina and electrographic signs of ischaemia tend to persist unchanged during long periods and adversely affect lifestyle in a considerable proportion of patients.

Dyspnoea on exercise in chronic heart failure is dissociated from hyperventilation

S W Davies, S L Jordan, D P Lipkin
The Royal Free Hospital, London

Dyspnoea is a major symptom limiting exercise in patients with chronic heart failure (CHF). In 20 patients with CHF (New York Heart Association grade II-III) the sensation of dyspnoea was assessed during progressive treadmill exercise using a 100 mm visual analogue scale (VAS). Mixed expired gas was analysed by mass spectrometer and online computer to calculate ventilation and oxygen consumption, and each patient was tested on at least two occasions. In 45/46 tests the dyspnoea VAS increased monotonically during exercise and decreased smoothly during the recovery phase. Exercise duration, peak oxygen consumption, peak ventilation, and peak dyspnoea VAS were all reproducible on repeat testing (mean difference (SD of differences): $-0{\cdot}9$ (0·5) min, $-0{\cdot}46$ (2·09) ml/kg/min, $-1{\cdot}0$ (2·9) l/min, -2 (3) mm respectively). The time course of changes in dyspnoea VAS during a test differed from the time course of increased ventilation: (a) the peak dyspnoea VAS score coincided with peak ventilation in only 57% of tests, occurring 15–120 seconds later in the other tests, when ventilation was falling; (b) at corresponding values of oxygen consumption during exercise and recovery phases ventilation in the two phases was similar, but the dyspnoea VAS was 11 (15) mm higher during recovery than during exercise; (c) in 17% of tests ventilation remained increased for $\geqslant 2$ minutes after the dyspnoea VAS had returned to baseline.

This dissociation between the ventilatory response to exercise and the dyspnoea VAS score suggests that the sensation of breathlessness in CHF cannot simply be explained by a sense of increased minute ventilation.

Silent ischaemia and QT prolongation in diabetic men with autonomic neuropathy

J J O'Sullivan, R Conroy, T McKenna, B Maurer
Department of Cardiology, St Vincent's Hospital, Dublin, Republic of Ireland

Autonomic neuropathy is associated with an increased frequency of silent myocardial infarction and sudden death. The prevalence of silent ischaemia in diabetic patients is unknown. We studied 34 diabetic men: 17 with evidence of autonomic neuropathy (group A) and 17 with normal autonomic reflexes (group B). There was no significant difference between the groups in age, risk factors, or anginal history. We used five autonomic tests and all patients had continuous 24 hour ambulatory electrocardiographic monitoring. Silent ischaemia was found in 64·7% (95% CI 38·3 to 85·7%) in group A and 5·9% (95% CI 0·15 to 28·69%) in group B. The QT interval was measured at rest and during the Valsalva manoeuvre in six men in each group. Group A showed a significantly longer QT interval for a given increase in RR interval ($p = 0·011$) than that measured in group B.

These findings may help to explain the increased frequency of sudden death in diabetic patients with autonomic neuropathy.

Non-invasive measurement of cardiac output during acute myocardial infarction by electrical bioimpedance cardiography

I N Findlay, D Northridge, J T Wilson, Esther Henderson, J Christie, H J Dargie
Cardiac Department, Western Infirmary, Glasgow

A reliable non-invasive technique for measuring cardiac output in acute myocardial infarction is described. We used the technique of electrical bioimpedance to measure cardiac output in 26 patients within 12 hours of the onset of chest pain. Cardiac output determined from the change in transthoracic impedance (TTI) was compared with that measured with Swan-Ganz catheter and thermodilution (TD). Mean (SD) cardiac output was 4·1 (1 1) (range 2·1–6·2) l/min by thermodilution and 4·1 (1·2) (range 1·1–6·2) l/min by TTI ($p = \mathrm{NS}$), ($r = 0·86$, $p < 0·0005$, $y = 1·06 \times - 0·4$, SEE 0·7 l/min). Mean stroke volume was 50 (18) ml by thermodilution and 48 (20) ml by TTI ($p = \mathrm{NS}$), ($r = 0·93$, $p < 0·0005$, $\mathrm{TTI} = 1·06\mathrm{TD}–4$, SEE 8 ml). Since the measurement of stroke volume by TTI is based on assumptions about thoracic volume and body surface area this was corrected for. The stroke volume index showed a similar close relation—stroke volume index was 27 (9) by TD and 26 (11) ml/m^2 by TTI ($p = \mathrm{NS}$), ($r = 0·93$, $p < 0·0001$, $\mathrm{TTI} = 1·05\ \mathrm{TD} - 2$, SEE 4 ml/m^2). The reproducibility of cardiac output by TTI was determined in 10 patients with repeat assessment after 30 minutes. Cardiac output was 4·2 (1·5) *v* 4·1 (1·4 l/min, mean difference = 0·13 l/min, 95% confidence limits 0·24 l/min, coefficient of variation 2·7%, $r = 0·99$, $y = 0·96 \times + 0·1$, SEE 0·14 l/min.

Measurement of cardiac output by electrical bioimpedance is highly reproducible, comparable with thermodilution, and offers the possibility of rapid non-invasive determination of cardiac function during acute myocardial infarction.

Fitness and coronary risk factors

S W Davies, T M Emery, M I L Watling, D Macfarlane, A G Shaper, D P Lipkin
The Royal Free Hospital, London

Exercise capacity and the level of regular exercise have been related to the incidence of coronary heart disease in surveys. We therefore examined the relation between exercise capacity and coronary risk factors in healthy untrained men to determine the pattern of association. Nine hundred and twelve men aged 25–67 (mean 42) without evidence of cardiac or pulmonary disease were assessed for coronary risk factors. Exercise capacity was determine by meausing maximal oxygen consumption ($\mathrm{Vo_2max}$) during progressive bicycle exercise; $\mathrm{Vo_2max}$ ranged from 28 to 85 ml/kg/min. There were correlations between $\mathrm{Vo_2max}$ and serum cholesterol ($r = -0·23$, $p < 0·0001$), triglyceride ($r = -0\ 38$, $p < 0·0001$), and diastolic blood pressure ($r = -0·27$, $p < 0·0001$). Systolic blood pressure and blood glucose were not related to $\mathrm{Vo_2max}$. These significant relations persisted after adjustment for age and for body mass index by multiple linear regression analysis. Regression analysis of the data suggested that a fitter subject in whom exercise capacity (Vo_2max) was increased by 10 ml/kg/min would have reductions in serum cholesterol (by 0·3 mmol/l) triglyceride (21% lower), and diastolic blood pressure (3 mm Hg lower). After adjustment for age and obesity these values are only 0·2 mmol, 17%, and 1·5 mm Hg respectively.

These independent relations between fitness, blood lipids, and diastolic blood pressure are small, and therefore any effects of fitness and exercise on coronary risk are likely to be direct, and independent of changes in the levels of the conventional risk factors.

Coronary disease in Asians associated with high insulin and C-peptide concentration

L Hughes, A Lahiri, E B Raftery
Northwick Park Hospital, Harrow, Middlesex

In the United Kingdom the morbidity and mortality from ischaemic heart disease (IHD) are higher in immigrants from the Indian subcontinent (Asians) than in whites. Many cardiovascular risk factors, however, including cholesterol concentration, blood pressure, and smoking rates are lower in Asians, but diabetes and impaired glucose tolerance are more common in Asians. It has been suggested that insulin resistance is a common pathological basis for both diabetes and IHD. Blood samples were taken from 76 white and 74 Asian patients between six months and two years after infarction and their controls. Cholesterol concentrations were higher in white patients 6·23 (1·04) mmol/l than in their age-matched white controls 5·65 (1·11) mmol/l ($p <$ 0·005) or in Asian patients 5·78 (0·99) mmol/l ($p <$ 0·01). Triglyceride concentrations ($p <$ 0·005) and insulin and C-peptide concentrations ($p <$ 0·0001) were significantly higher in patients than in controls and higher in Asians than in whites ($p <$ 0·001). Additionally, patients and controls with impaired glucose tolerance had significantly higher concentrations than those with normal blood glucose. Insulin concentrations correlated inversely with high density lipoprotein cholesterol $r = -0{\cdot}31$ ($p <$ 0·02). Among Asians 32% of patients and 28% of controls were diabetic or had impaired glucose tolerance ($p =$ NS), and mean blood glucose, fructoseamine, and glycosylated haemoglobin concentrations were not higher in patients than in controls.

This suggests that insulin resistance was greater in patients with IHD and greater in Asians than in whites. This mechanism may have increased cardiovascular risk directly or by adverse changes in lipids.

Is silent ischaemia common in patients with coronary artery disease and angina receiving standard medical treatment?

D Mulcahy, Jennifer Keegan, Christine Wright,
Jane Sparrow, Amanda Park, K Fox
National Heart Hospital, London

It has been suggested that many patients with angina may have frequent daily epsiodes of silent myocardial ischaemia (SMI). This assumption is based on the results of studies in selected patients off routine antianginal medications; however, in clinical practice most patients with coronary artery disease (CAD) and angina receive medical treatment from their physicians. We studied the frequency and characteristics of SMI in 114 patients (101 men), mean age 55·5 yr (range 30–74 yr) with documented CAD (21 single, 44 two, 49 three vessel disease) and angina who were on standard antianginal treatment. Patients underwent treadmill exercise testing ($n = 109$) and 48 hours of ambulatory ST segment monitoring (total = 5125 h). Sixty nine (63%) patients had a positive exercise test for ischaemia, and 38 (33%) had a total of 154 episodes of SMI during ambulatory monitoring. There was no significant relation between the frequency of SMI and the severity of CAD or angina, history of previous myocardial infarction, or number of antianginal medications taken. SMI was strongly related to a positive exercise test ($p <$ 0 0001), and was rare and of short duration in those with a negative exercise test. The circadian pattern of SMI showed a peak in the evening hours. Seventy six (67%) patients had no SMI on 48 hours of monitoring. Only four (3·5%) had frequent daily episodes ($\geqslant$ 5 days) and < 10% of patients had > two episodes a day.

Frequent daily episodes of silent ischaemia are rare in medically treated patients with CAD and angina and only 33% of this unselected group of patients had any episodes recorded during 48 hours of ambulatory monitoring.

Monitoring oxygen transport in cardiogenic shock

J E Creamer, J D Edwards, P Nightingale
University Hospital of South Manchester

Critically low values of mixed venous oxyhaemoglobin saturation ($S\bar{v}o_2$) occur in cardiogenic shock but there are no data on oxygen consumption (Vo_2) or delivery (Do_2) or on their response to treatment. We prospectively studied 19 patients (12 men and seven women, mean age 60 years) with clinical features of cardiogenic shock after acute myocardial infarction. Femoral and pulmonary artery catheters were inserted before any treatment except correction of hypoxaemia (eight needed mechanical ventilation), defibrillation (three patients), or pacing (five patients). Three patients had normal haemodynamic and oxygen transport measurements despite simultaneous clinical evidence of shock. They recovered with no further treatment. The other 16 patients were given fluid volume replacement and dobutamine (36·5 (24·5) µg/kg/min) as necessary. Vo_2 was maintained even when Do_2 was reduced to 160 ml/min/m^2. Mean cardiac index increased from 1·3 (0·4) to 2 5 (0·4) l/min/m^2 ($p < 0{\cdot}001$). Mean Do_2 increased from 222 (65) to 384 (94) ml/min/m^2 ($p < 0{\cdot}001$) and mean Vo_2 from 104 (32) to 125 (24) ml/min/m^2 ($p < 0{\cdot}05$). Mean $S\bar{v}o_2$ increased from 52 (14) to 68 (8)% and mean oxygen extraction ratio fell from 50 (15) to 32 (6)% ($p < 0{\cdot}001$). There was no correlation between cuff systolic blood pressure and mean arterial pressure. Thirteen patients survived.

Cardiogenic shock cannot be adequately managed without invasive monitoring of mean arterial pressure. Increases in Do_2 lead to only small increases in Vo_2 but to large increases in $S\bar{v}o_2$ as oxygen extraction ratio falls, suggesting improved tissue oxygenation. Monitoring of oxygen transport variables may help to determine therapeutic goals and improve outcome in cardiogenic shock.

Effect of initial lesion type on the results of coronary angioplasty

R Balcon, M Rothman, A Gershlick, C Layton, A Mishra
London Chest Hospital, and National Heart and Lung Institute, London

Coronary angioplasty inevitably causes some arterial injury, which may result in dissection of the vessel and thrombus formation. These are the most important causes of acute failure of the procedure and may also play a role in restenosis. Pre-existing evidence of plaque irregularity may increase this problem. The extent to which this occurs has been examined by evaluating the results of coronary angioplasty according to its presence or absence. Coronary lesions were retrospectively classified by an independent observer to divide patients undergoing coronary angioplasty into a group of 242 in whom all of the treated stenoses were smooth and 68 in whom they were all irregular. Two hundred and forty eight (82 9%) of the 299 smooth stenoses were successfully dilated compared with 48 (64%) of the 74 irregular lesions ($p < 0{\cdot}001$). Acute occlusion occurred in nine (12%) patients in the group with irregular lesions compared with 14 (4·7%) in those with smooth lesions ($p < 0{\cdot}02$). The average residual stenosis of the successfully dilated lesions was 18·5% in the irregular group and 23·0% in the smooth ($p < 0{\cdot}03$). At follow up 72·8% of the patients in the smooth group improved by two or more clinical angina grades compared with 58·5% in the irregular group ($p < 0{\cdot}05$). Follow up coronary surgery was needed in 14·6% of the irregular group and 5·3% of the smooth group ($p < 0{\cdot}05$).

Angiographic evidence of plaque disruption before coronary angioplasty may permit a greater degree of dilatation but is associated with a lower primary success rate, a higher acute occlusion rate, less symptomatic relief, and a greater need for later coronary sugery.

Stent implantation for the treatment of coronary artery bypass graft stenosis

K J Beatt, O Kamp, H Suryapranata, R Geuskens, P W Serruys
Thoraxcenter, Erasmus University, Rotterdam, The Netherlands

The long term success of balloon angioplasty in coronary artery bypass grafts is limited by the high recurrence rate of the initial stenosis. Eighteen self-expanding intravascular stents were implanted in 12 patients after balloon dilatation of a coronary artery bypass graft stenosis, and the immediate results were assessed by quantitative coronary angiography. The mean age of the group was 61·3 (43–75) years and the age of the bypass graft 65·9 (62–125) months. In 10 patients the procedure was elective as a measure to prevent restenosis and in one the stent was implanted after dissection and the dislocation of atheromatous material in order to improve the immediate haemodynamic result, and so avoid or delay the need for bypass surgery. The mean unconstrained diameter of the stent was 4·1 (3·0–5·0) mm, implanted into grafts with a mean diameter of 3·3 (2·1–4·4) mm. The implantation was proximal in three cases and in the middle of the bypass graft in nine cases. In five cases the stent was implanted in the distal portion either before or after the first jump and in two patients the device was positioned so as to involve the distal anastomosis—one straddling an end-to-side anastomosis and one a side-to-side anastomosis. The minimal lumen diameter was 1·4 (0·7–2·2) mm before angioplasty, 2·1 (0·6–3 3) mm after, and 2·6 (1·8–3·7) mm after stent implantation.

So far there have been more than 44 stents implanted into the coronary artery vein grafts of 29 patients in five centres in Europe. This has been achieved without technical difficulty or procedure related complication, and the implanted device seems to improve the haemodynamic result. Detailed follow up studies are needed to determine how effective this device will be in the long term treatment for coronary bypass stenosis.

Simple and complex coronary angioplasty with a Monorail system

G Bergman, B Meany, Jennie Metcalfe, S Thomas, G Jackson, D E Jewitt
Cardiac Department, King's College Hospital, London

Coronary angioplasty of single, multiple, and complex lesions was attempted with a Monorail system in 560 patients. The potential advantages of the Monorail design relate to its short over-the-wire tracking segment. Primary success was achieved in 92% with a complication rate of only 4%. These results compare favourably with 87% success rate and a 3·8% complication rate in 250 patients (264 lesions) who had angioplasty before the Monorail system became available. The major limitation of this system has been looping of the guide wire, behind the tracking segment, resulting in locking of the balloon and wire. This has been overcome in the new generation of (Piccolino) balloons which have the further advantage of an extremely low profile. Poor tracking was probably responsible for failure to cross eight distal lesions, which were successfully dilated by a different system. This system design allowed serial dilatation, initially with a small balloon, and then with a more appropriately sized one, in 8% of cases, without the difficulty of use of an exchange wire. In 30 bifurcational lesions successful dilatation of both limbs of the stenosis was achieved in 94%. A single balloon was passed serially over two pre-positioned wires, allowing ease, safety, and economy. Excellent distal visualisation facilitated procedural decision making while maintaining access to the distal vessel.

A Monorail system provides an over-the-wire balloon dilatation system with the advantages of ease of exchange, low profile, and good visualisation, but the system may not be ideal for distal or tortuous vessels.

Measurement of inflated balloon size during angioplasty: importance of balloon material, artery size, and inflation pressure

W J Penny, J H Chesebro, Magda Heras, M Bell, D R Holmes, R E Vlietstra
Mayo Clinic, Rochester, Minnesota, USA

Angioplasty balloon size may be affected in vivo by factors other than the manufacturer's in vitro sizing. Factors affecting balloon size were tested in 54 inflations in 18 patients. Dimensions were analysed by a computer based quantitative angiographic system. At the same inflation pressure (4·9 (0·2) atm), polyethylene terephthalate (PET) balloons were larger than polyethylene (PE) balloons, inflating to 92 (2)% *v* 83 (3)% of the manufacturer's size (p = 0 01). Three mm PET balloons were larger than 3 mm PE balloons (2·7 (0·04) *v* 2·5 (0·04) mm, p < 0·02). PE but not PET balloons increased in size from first (2·3 (0·1)) to final inflation (2·6 (0·1) mm, p = 0·03). Balloon size correlated with inflation pressure (r = 0·73, p = 0·004) and cross sectional area of the normal artery (r = 0·87, p = 0·001) but not of the stenosis. Balloon oversizing was tested in pig carotid arteries in vivo. Eight mm balloons (6 atm) were smaller (5·2 (0·1) mm; range 4–6·7 mm, n = 60) than the manufacturer's size (p = 0·0001). Balloon size correlated with artery size (r = 0 43, p = 0·001). In equal size arteries PET balloons were larger (5·3 (0·1) mm, n = 30) than PE balloons (5·1 (0·1) mm, n = 30 p < 0·01). Inflated (6 atm) in pig coronary arteries in vivo polyvinylchloride (PVC) balloons (n = 30) were smaller than the manufacturer's size (3·0 (0·1) *v* 3 3 (0·1) mm, p = 0·0001) and correlated with artery size (r = 0·72, p = 0·0001). Four mm PVC balloons (n = 10) ranged from 2·6 to 3·8 mm, depending on the artery size (r = 0·76, p = 0·01).

In vivo, the inflated angioplasty balloon size depends on the artery size, the balloon material, and the inflation pressure, and the size achieved in vivo is less than the manufacturer's in vitro size. This has important implications for optimum balloon selection.

Laser-generated tissue debris causes considerable platelet aggregation in vitro

A J I Scriven, A W Nathan
St Bartholomew's Hospital, London

Laser ablation generates tissue debris, and this study was performed to examine the effects of debris on platelet function in vitro. Segments of normal and atheromatous human aorta, and of human and porcine thrombus, were suspended in 1 ml saline. These were exposed to energy from a flashlamp-pumped, pulsed dye laser operating at 504 nm. The energy was delivered via a 600 μm quartz optical fibre, and the total energy per segment was increased by increments from 4 J to 60 J. Exposure of the tissue segment to laser energy generally resulted in the saline becoming turbid. The turbid suspension was divided into two samples; one was centrifuged to form a particle free supernatant. Samples (20 μl) of the suspension or the supernatant were added to 500 μl of human or rabbit platelet rich plasma in a Born aggregometer by standard methods. Debris suspension from normal aorta caused modest (< 30%) aggregation, but atheromatous debris had no effect. By contrast, both debris suspension and supernatant from thrombus consistently caused considerable (65–70%) dose-related aggregation even when the total energy delivered was modest (for example 15 J). The aggregation reaction provoked by the suspension was irreversible. These effects were not inhibited by heparin 0·1–10 U/ml, aspirin 0·2–2 mmol/l, or by 0·03 ng/ml iloprost, a synthetic prostacyclin analogue. However, iloprost 0·3 and 3 ng/ml reduced aggregation to 42% and 0% of control respectively ($p < 0\ 05$).

Debris from thrombus caused considerable platelet aggregation in vitro. These findings may be relevant to laser coronary angioplasty and require further study in vivo.

Cardiac rehabilitation after open heart surgery: a surprising fact

F Black, B Foley, P Crean, M Walsh
Trinity Cardiology, St James's Hospital, Dublin, Republic of Ireland

The population of patients undergoing open heart surgery at our institution is divided into an urban group of patients who attend a cardiac rehabilitation programme and a rural group who for geographical reasons do not. The aim of this study was to determine the effect of cardiac rehabilitation on (a) the interval before return to work and (b) changes in employment pattern after open heart surgery. One hundred and eleven patients were interviewed. Fifty three (39 men, mean age 50·6 years and 14 women, mean age 58 3) attended the cardiac rehabilitation programme. Fifty eight patients (51 men, mean age 58·1 and seven women, mean age 55·9) had not. The mean interval before return to work was 22·2 (17·4) weeks in those in the rehabilitation group and 13·4 (7·68) weeks in the group who had not ($p < 0{\cdot}005$). In the rehabilitation group five who were unemployed before surgery remained unemployed after surgery and six others became unemployed. In the non-rehabilitation group three who were unemployed before surgery remained unemployed after surgery and six others became unemployed. In the cardiac rehabilitation group one proceeded to early retirement (< 60 years), as did two in the non-rehabilitation group.

Surprisingly, those who attended the cardiac rehabilitation programme took significantly longer to return to work than those who did not attend the programme.

The use of trained autologous skeletal muscle for long term counterpulsation in a sheep model

C W Pattison, Debbie Cumming, Carol Lovegrove, D G Clayton-Jones*, M J Dunn, G Goldspink*, M Yacoub
Department of Cardiothoracic Surgery, National Heart and Lung Institute, London, and *Royal Veterinary College, London

There is a need for the development of long term circulatory support in patients with severe chronic heart failure. Effective aortic counterpulsation was produced in 10 sheep by wrapping the mobilised and pedicled latissimus dorsi around the proximal descending aorta followed by pulse train electrical stimulation at 35 Hz. The blood supply of the flap, monitored by surface electrical impedance in five animals, fell to 20% of normal during the first day and returned to 62% of normal after 72 hours. Histological examination of the flap from animals killed at different periods up to four weeks after the procedure showed no evidence of muscle damage or fibrosis. Fluorescent immunocytochemistry with monoclonal antibodies against slow and fast myosin isoforms showed a fourfold increase in the proportion of type I fatigue resistant muscle fibres. Enzyme histochemistry confirmed the shift in fibre type by measuring the associated metabolic changes.

Long term effective counterpulsation by entirely autologous skeletal muscle is feasible, safe, and associated with appropriate structural and metabolic changes in the skeletal muscle.

Colour flow mapping in the detection of intracardiac fistulas after aortic valve surgery for endocarditis

J Smyllie, G R Sutherland, M van Daele,
J R T C Roelandt
Thoraxcentre, Rotterdam, The Netherlands

Previous reports suggest that an intracardiac fistula (ICF) is a rare complication of aortic valve replacement after infective endocarditis (IE). The diagnosis of ICF in this situation is difficult by clinical criteria alone and traditionally is based on angiography. More recently colour flow mapping (CFM) has become the diagnostic technique for the recognition of complex intracardiac shunting. Cross sectional echocardiography and CFM were used to study 40 consecutive patients who had undergone aortic valve replacement for active IE, in order to determine the incidence and spectrum of ICF in such patients. In 7/40 (18%) CFM detected an ICF by showing the origin and extension of an abnormal turbulent jet lesion between the left ventricular outflow tract and left atrium (three patients) left ventricular outflow tract and right atrium (two patients), aorta and right ventricle (one patient), and aorta and right atrium (one patient). The diagnosis was clinically unsuspected in six cases. Cross sectional echocardiography was diagnostic in only one patient. Before the CFM study, pulsed and continuous wave Doppler were diagnostic in only one case. Despite persistence of the ICF five patients remain symptom free six months to five years after operation; two have required reoperation.

We conclude that ICF is much more common after aortic valve replacement for active IE than previously suspected. In our experience CFM was the only diagnostic technique which provided accurate information on the presence of such lesions and in our opinion CFM is essential in both the intraoperative and postoperative evaluation of all cases of aortic valve replacement in active endocarditis.

The cerebral function analysing monitor as the sole predictor of neurological damage after coronary artery bypass surgery

M Nevin, A C F Colchester, S Adams, J R Pepper
Cardiothoracic Unit, St George's Hospital and Atkinson Morley's Hospital, London

There is growing evidence that up to 80% of patients recovering from coronary artery bypass surgery may show subtle neuropsychometric changes that cause concern to the patient and family. Sixty five patients who underwent coronary artery bypass surgery had a detailed neuropsychometric assessment before operation and twice in the first week after operation. Throughout the operation a cerebral function analysing monitor (CFAM) was used for continuous monitoring of the parietal lobes. Thirty seven patients (57%) had an important neuropsychometric deficit and 86% of them also showed significant CFAM changes—most of which occurred immediately after the start of perfusion. Five of these 37 patients showed no CFAM changes—a false negative rate of 15%. Of 28 patients with no neuropsychometric deficit, six showed significant CFAM changes—a false positive rate of 21%.

We found that careful observation of the CFAM trace gave a sensitivity of 86% and a specificity of 79% for subsequent neuropsychometric changes. Remarkably, all patients whose CFAM traces showed more than one significant change developed an important neuropsychometric deficit in the first week after operation.

Middle cerebral artery microembolism: a comparison of bubble oxygenator with arterial line filter and membrane oxygenator alone

S Griffin, W Pugsley, T Treasure
Department of Cardiothoracic Surgery, Middlesex Hospital, London

Microemboli can be detected in the arterial circulation during cardiopulmonary bypass. These can be detected with a transcranial Doppler transducer and they are likely to be responsible for the microvascular occlusions seen in the retina and to contribute to neuropsychological changes shown after cardiac surgery. Twenty patients undergoing either routine coronary artery bypass grafting (17), valve replacement (2), or repair of ventriculoseptal defect (1) were allocated either to a Harvey 1700 bubble oxygenator with a 40 μm Pall arterial line filter or to a Cobe hollow fibre membrane oxygenator with no in-line arterial filter. All cases received pulsatile perfusion with core cooling to 28°C. Microembolic events were measured by the counting of additional noises over the pattern of normal pulsatile flow; these were confirmed by reference to the visual waveform generated on the screen. Median bypass time was 61 minutes (range 45–95) for the bubbler group and 77 minutes (range 50–115) for the membrane group. The median number of microembolic events per 15 minutes of bypass was 18 events (range 6–54) for the bubble oxygenator and 16 (range 10–65) for the membrane group. There was no significant difference between the groups (Mann-Whitney $p = 0.4$).

We conclude that the previously reported excess of microemboli from bubble oxygenators compared with membrane oxygenators was abolished when a 40 μm arterial line filter was used with the bubble oxygenator.

Tricuspid regurgitation and pulmonary artery pressure five years after implantation of mitral bioprostheses

S Ikram, R Maire, P A Lewis, O Odemuyiwa,
S V Lo, C Hilton, R J C Hall
University Hospital of Wales, Cardiff and Freeman Hospital, Newcastle upon Tyne

Seventy one patients (median age 60, 22 men) underwent mitral valve replacement (MVR) with tissue valves (85% for rheumatic disease). There were five early deaths (at operation or within 30 days) and 10 late deaths (up until 15 February 1988), leaving 56 long term survivors. The five year survival rate for all patients was 83%. The mean preoperative systolic pulmonary artery pressure (PAP_s) was 53 mm Hg (95%CI 48 to 57) for the 56 long term survivors and was 76 (95%CI 60 to 91) for the late deaths; the respective pulmonary vascular resistances were 318 (95%CI 255 to 380) and 689 dyn s cm^{-5} (95%CI 395 to 983). Forty of the 56 survivors had clinical, echocardiographic, and Doppler assessment at least five years after operation (median 6·2 years). The New York Heart Association class improved in 32 patients, was identical in seven, and was worse in one. The most striking non-invasive feature at follow up was that tricuspid regurgitation (TR) was very common (32/40). This allowed non-invasive assessment of PAP_s, and in 14 patients the TR was sufficiently severe to be clinically significant. This high incidence of significant TR was not the result of persistent pulmonary hypertension because in 12 of the 14 patients with significant TR the PAP_s was $\leq$ 45 mm Hg (in five of these 12 patients PAP_s was $\leq$ 30). In the remaining two patients PAP_s was > 45 mm Hg. In the whole group with TR the median PAP_s fell from 50 before operation to 28 mm Hg at follow up (average fall = 22).

In the long term almost all patients with MVR show a reduction in PAP_s. A substantial number, however, have significant TR associated with normal or only mildly raised pulmonary pressures, suggesting an organic cause.

Cardiac abnormalities in patients with type IV mucopolysaccharidosis: Morquio syndrome

R M John, D Hunter, R H Swanton
Middlesex Hospital, London

Cardiac involvement has been reported in all forms of mucopolysaccharidoses but little note made of abnormalities specific to Morquio's syndrome. The Morquio-Brailsford syndrome (type IV mucopolysaccharidosis) is caused by a deficiency of N-acetyl hexosaminidase-6-sulphatesulphatase and results in the excretion of keratan sulphate in the urine. As in all other types of mucopolysaccharidoses, incompletely degraded glycosaminoglycans accumulate in various tissues. We report on the echocardiographic features of 10 patients (five men and five women; median age 12 5 years, range 3–40) with Morquio's syndrome. Six (60%) patients had echocardiographic evidence of cardiac abnormalities. Mitral valve thickening with prolapse producing mild to moderate mitral regurgitation on Doppler echocardiography was the most frequent abnormality, occurring in five patients. One of these patients had severe thickening of the mitral leaflet and annulus to the point of significant mitral stenosis (mitral valve gradient on Doppler echocardiography was 6 mm Hg). Aortic valve involvement with mild aortic regurgitation was evident in three patients (as isolated abnormality in one patient and in conjunction with mitral valve disease in two). Myocardial involvement characterised by ventricular hypertrophy occurred in two patients with biventricular hypertrophy out of proportion to valve abnormality in one patient and considerable apical left ventricular hypertrophy in another. The frequency of cardiac abnormalities increased with age.

Progressive valvar and myocardial disease is common in this rare group of patients and although corrective cardiac surgery may not always be necessary or feasible, cardiac follow up and bacterial endocarditis prophylaxis are warranted.

Prevalence of ventricular arrhythmias in patients with left ventricular hypertrophy caused by aortic valve disease

A Al-Riyami, P W Macfarlane, S M Cobbe
Department of Medical Cardiology, Royal Infirmary, Glasgow

It has been suggested that patients with left ventricular hypertrophy are at risk of sudden death from ventricular arrhythmias. We studied the prevalence of ventricular arrhythmias and of an abnormal signal averaged electrocardiogram (SAECG) in 35 patients with electrocardiographic left ventricular hypertrophy secondary to aortic valve disease. The mean age was 62 years (range 41–78). The dominant lesion was aortic stenosis in 29 patients, with a mean systolic gradient of 69 (range 30–115) mm Hg, and aortic regurgitation in six. Mean left ventricular mass index by echocardiography (Penn convention) was 217 gm^2 (range 91–343, normal range < 132). Forty eight hour ambulatory electrocardiographic recording showed < 10 ventricular premature depolarisations (VPDs) per hour in 29, 10–30 VPDs/h in five, and > 30 VPDs/h in two patients. Three patients had > 10 ventricular couplets/24 h, and three had salvoes of non-sustained ventricular tachycardia up to four beats in duration. The SAECG was assessed for the following abnormalities: filtered QRS duration > 120ms, amplitude of last 40 ms of filtered signal $< 25\ \mu V$, and duration of low amplitude signal > 38 ms. Abnormalities were found in 6, 2, and one patient respectively, but only two patients had abnormalities by two or more criteria. Of the five patients with frequent couplets or non-sustained ventricular tachycardia, only one had an abnormal SAECG.

Despite the presence of severe left ventricular hypertrophy in these patients, the prevalence of repetitive ventricular arrhythmias was low and could not be predicted by signal averaged electrocardiography.

Ventricular stroke work loss: an alternative method of quantifying the severity of aortic stenosis

D C Sprigings, J B Chambers, T Cochrane, J Allen, M M Black, G Jackson
King's College Hospital, London

The systolic pressure gradient across the aortic valve (SPG) is an inaccurate index of stenosis if cardiac output is low or there is appreciable aortic regurgitation. Because aortic stenosis results in loss of left ventricular stroke work (LVSW) (because of friction through the valve and turbulent flow in the ascending aorta), the percentage of LVSW that is lost may be a measure of the severity of stenosis. We compared the percentage loss of LVSW and maximum aortic orifice area (OA) (measured by planimetry of videotape) in a computer controlled pulse duplicator. Thirteen valves were studied (nine human aortic valves obtained at necropsy and four bioprosthetic valves) at stroke volumes from 40 to 100 ml, giving 57 data points. OA ranged from 0·3 to 2·8 cm^2 and mean SPG from 3 to 84 mm Hg. The percentage loss of LVSW, calculated as mean SPG divided by mean LV systolic pressure × 100, was 7–68% and showed a close inverse correlation with OA ($r = -0{\cdot}88$, $p < 0{\cdot}00001$). It was only weakly correlated with flow ($r = 0{\cdot}15$, $p = 0{\cdot}25$).

We conclude that the percentage loss of left ventricular stroke work reflects aortic valve area over a wide range in this model. It may be a clinically useful index of aortic stenosis: it has the important advantage over the Gorlin formula of not requiring measurement of cardiac output.

The relative values of intraoperative epicardial and transoesophageal echocardiography in mitral valve repair

A G Fraser, L van Herwerden, M E R M van Daele, E Bos, J R T C Roelandt, G R Sutherland
Thoraxcenter, Academisch Ziekenhuis Dijkzigt, Rotterdam, The Netherlands

Mitral valve repair is preferable to replacement in patients with appropriate valve morphology. In our experience, preoperative investigations have limitations in identifying valves suitable for repair, but intraoperative echocardiography should both identify such valves and provide immediate assessment of surgical results. We studied the relative values of epicardial (EE) and transoesophageal (TEE) echocardiography in 15 patients scheduled for conservative valve surgery. Excellent images were obtained with both techniques in all subjects. In 13, both EE and TEE showed prolapse of one mitral leaflet (anterior six, posterior seven), but the mitral valve could be imaged in multiple planes only with EE. Thus EE and not TEE showed prolapse or failure of coaptation restricted to a single scallop of either leaflet and thus indicated the type of valvoplasty required. Colour flow mapping (CFM) by TEE was better than EE in showing mitral regurgitant jets, which were eccentric in all patients with prolapse. Five patients required valve replacement. In the others, TEE CFM showed no significant residual regurgitation through the repaired valves; assessment by EE was limited by flow masking of the left atrium by prosthetic material. Contrast echocardiographic assessment of mitral regurgitation via left ventricular puncture during EE caused ventricular arrhythmias ($n = 5$) and gave images of limited value.

We conclude that EE is the best technique for the intraoperative evaluation of mitral valve morphology, and that transoesophageal CFM is the most useful technique for identifying regurgitation. Contrast echocardiographic assessment of valve regurgitation has been superceded by CFM.

Ten year results of a randomised trial of the Björk-Shiley, Hancock, and Carpentier-Edwards prostheses

P Bloomfield, D J Wheatley, R J Prescott,
H C Miller
Royal Infirmary of Edinburgh, Edinburgh

From 1975 to 1979, 540 patients undergoing heart valve replacement were entered into a randomised trial and received either a Bjork-Shiley mechanical (BS) or porcine (Hancock or Carpentier-Edwards) prosthesis: 210 underwent aortic valve replacement (AVR), 262 mitral valve replacement (MVR), and 60 AVR + MVR. Only eight underwent tricuspid valve replacement and these were excluded from further analysis. Mean follow up was 10·4 (range 7·5–12 5) years. Actuarial survival at 10 years was 56·5 (2·2)% for all patients, 65·2 (3·3)% after AVR, and 50·1 (3 2)% after MVR, with no significant difference between the prostheses. Reoperation for valve failure was necessary significantly more often in patients with porcine (53) than with BS prostheses (17)—mainly because of cusp failure of porcine prostheses more than five years after implantation. Reoperation or cardiac death were taken as end points for actuarial analysis and were significantly less frequent for patients receiving the BS prosthesis when the whole series and the subgroup undergoing MVR were considered, but not in the subgroup receiving an AVR. All patients with BS prostheses received anticoagulants. Bleeding complications were significantly more common in patients with BS prostheses (28) than in those with porcine prostheses (15). Death, bleeding complications, reoperation, embolism, and bacterial endocarditis were taken as end points for an actuarial analysis of "event free" survival; there was a non-significant trend in favour of the BS prosthesis when the whole series and the subgroup undergoing MVR were considered, but no discernible trend after AVR.

Balloon dilatation of the mitral valve for "inoperable" mitral stenosis

T R D Shaw, D McAreavey, A R Essop, C S Song
Department of Cardiology, Western General
Hospital, Edinburgh

In the United Kingdom many patients with mitral stenosis are elderly and have non-cardiac disease. Seventeen of 50 patients undergoing balloon dilatation of the mitral valve had additional medical problems judged to make them at high risk for cardiac surgery. The main contraindication to operation was severe obstructive airways disease in eight, very poor left ventricular function in four, multiorgan failure in three, intrathoracic adhesions in one, and psychiatric disorder in one. Six required urgent dilatation because their clinical condition was critical; 11 procedures were elective. The mitral valve was heavily calcified in nine and had moderate/mild calcification in four. Balloon dilatation of the mitral valve was achieved in all 17 patients with a 25 mm balloon (n = 13) or double balloon dilatation (n = 4). The mitral valve gradient fell from 13·9 to 5·5 mm Hg, cardiac output rose from 2·84 to 3·58 l/min, and valve area increased from 0·71 to 1·54 cm^2. Mean left atrial pressure was reduced from 24·3 to 15·1 mm Hg. Right ventricular systolic pressure fell from 66 to 54 mm Hg (all $p < 0{\cdot}05$). Thirteen patients had a final valve area of $> 1{\cdot}2\ \text{cm}^2$ and nine of $> 1{\cdot}5\ \text{cm}^2$. No major complications occurred during the procedures. Two patients died shortly after balloon dilatation. Both had additional respiratory disease and both had required artificial ventilation. In retrospect more vigorous use of ventilation might have been of benefit to these two patients. Of the remaining 15 patients, 14 had an improvement in symptoms.

Balloon dilatation of the mitral valve can be a helpful alternative treatment in patients who are unsuitable for operation.

Coronary lesions after thrombolysis: irregularity predicts need for urgent intervention

S W Davies, B Marchant, J P Lyons, A D Timmis,
C Layton, M T Rothman, R Balcon
The London Chest Hospital, London

After thrombolysis there is a high incidence of early recurrent angina and of reinfarction. Quantitative analysis of coronary lesion morphology was performed in 72 consecutive patients, who underwent elective angiography two to eight days after receiving streptokinase within six hours of infarction. All were clinically stable at the time of angiography and remained on heparin infusion for at least four days after thrombolysis. After angiography but during the same admission, 15 developed prolonged episodes of angina at rest. Four settled medically but 11 required urgent intervention—angioplasty in eight and coronary artery bypass grafting in eight, at between two and 10 days after thrombolysis. There were no differences between those developing unstable angina and those with a stable in-hospital course in term of age, sex, extent of coronary disease, or left ventricular function. There was, however, a significant difference in the ulceration index (UI) of the lesion in the infarct related artery: unstable course 10·4 (14·0) *v* stable course 3·8 (2·8) (p < 0·001). There were no differences in the severity of stenosis, length of diseased segment, symmetry/eccentricity, shoulder, location at branch point, globular or linear filling defects, or contrast staining. These data show that after thrombolysis the degree of irregularity of the infarct related artery is a critical determinant of clinical instability. When the UI was ⩾ 6 at angiography 11/19 subsequently developed unstable angina, whereas when the UI was < 6 only 4/53 did (p < 0·001). Other morphological features seem to have little predictive value.

Thus quantitative analysis of coronary lesion morphology defines a subset of patients at high risk of complications in whom intensive medical treatment is indicated.

Thrombolysis for acute myocardial infarction: Is there adequate provision in England?

J D Skehan, M L Cowley, C J Burrell, C W Barrett, P G Mills
The London Hospital, Whitechapel, London

The benefit of early thrombolysis in acute myocardial infarction is established. The provision of such treatment was studied in over one third of English Health Districts. Of 65 districts surveyed only 20 (31%) had a published policy available to junior medical staff. A policy was "in preparation" in 26 (40%) while 19 (29%) reported no plans for developing a policy. Formation of a district policy was not influenced either by thrombolytic trial participation or by the presence or absence of a district cardiologist. An age limit is stipulated in 43% of current policies, a time window in all (4 h, 6%; 6 h, 36%; 12 h, 14%; and 24 h, 44%), heparin in 43%, and aspirin in 98%. Thrombolytic agents were available in accident and emergency departments in only 27% of districts surveyed and in 41% of those with a published policy. At present streptokinase is the preferred agent in all districts, whether or not a formal policy exists. Expenditure on streptokinase has increased considerably but currently varies by a factor of up to 40 between districts and represents 0·5 to 20 treatments per month per 100 000 population. At the time of survey, trial drugs continued to offset costs in only a few districts.

Most health districts are responding to the requirement for thrombolysis in acute myocardial infarction but considerable variations remain in both policy guidelines and the number of patients being treated.

Serial intravenous bolus injections of recombinant tissue type plasminogen activator are associated with rapid recanalisation in patients with acute myocardial infarction

M I Khan, D R Hackett, E McFadden,
Felicita Andreotti, P Halson, G J Davies, A Maseri
Cardiovascular Unit, Hammersmith Hospital,
London

A rapid intravenous (IV) bolus injection rather than continuous infusion of a thrombolytic agent would facilitate pre-hospital coronary thrombolysis. We studied 24 consecutive patients with early evolving acute myocardial infarction within 6 h after the onset of chest pain. Patients were randomised to receive either an intravenous infusion of 70 MU (= 100 mg) recombinant tissue type plasminogen activator (rt-PA) over 1·5 h followed by an infusion of 35 MU over 5 h (group I, n = 11), or four bolus intravenous injections of 17·5 MU administered at 20 min intervals (group b, n = 13). The patency of the infarct related coronary artery (IRCA) was assessed by angiography before and during rt-PA administration and by recatheterisation at 24 h. The mean duration of chest pain at the start of rt-PA was 3·1 h (range 1·5–5·0) in group I and 3·0 h (1·5–5·0) in group B (p = NS). Acute recanalisation of the IRCA resulted in seven of 11 patients in group I and 10 of 13 in group B (p = 0·2); in one patient in group B the vessel had reoccluded by 24 h. Mean (SD) time from the start of rt-PA to full patency of the IRCA was 40 (7·2) minutes in group I and 28·1 (6·7) in group B (p = 0·2). There were no significant differences in the minimum IRCA lumen between group I and group B at 90 minutes (1·29 (0·6) *v* 1·20 (0·3) mm or at 24 h (1·54 (0·5) *v* 1·24 (0·2) mm). The maximum falls in fibrinogen were 59·5 (9·9)% and 47·3 (9·5) respectively (p = NS). Groin haematomas occurred in five patients in group I but in none in group B.

Bolus intravenous rt-PA seems to result in earlier recanalisation of the IRCA than intravenous infusion and is associated with fewer bleeding complications and less fibrinogen depletion. The findings of this pilot study suggest there is considerable scope for investigating the use of bolus dosing in larger groups of patients.

Circulating concentrations of free radicals in patients with myocardial infarction

P D Higham, C Bleasdale, A M Brown, S Saltissi, M J Jackson, C R K Hind
University Department of Medicine, Royal Liverpool Hospital, Liverpool

Experimental studies suggest that post-ischaemic myocardial dysfunction may be mediated in part by the generation of free radicals. First, the use of free radical scavenging agents has been shown to promote earlier recovery of myocardial function after induced ischaemia in animals. Secondly, recent studies of dogs by electron paramagnetic resonance spectroscopy have provided direct evidence of free radical production in reperfused myocardium. But this technique is not clinically applicable, and there are no data on human free radical production after myocardial infarction. Such free radicals can cause diene conjugation of native fatty acids (for example, the production of 9,11-linoleic acid (9,11-LA') from 9,12-linoleic acid (9,12-LA)). This property forms the basis of an assay of circulating free radical products by high performance liquid chromatography, the results of which are best expressed as a molar ratio of [9,11-LA']/[9,12-LA](%MR) (normal range 0·5–2·0). To investigate the behaviour of these free radical products after myocardial infarction, serial venous blood samples were taken every 24 hours after the onset of chest pain in 12 patients with definite myocardial infarction (seven men, five women; mean age 55·7 years, range 41–70 years). These samples were separated, stored at − 20°C, and later assayed in batches for %MR and creatine kinase-MB (CK-MB) measurements. We found that 11 of the patients had a raised %MR (mean peak value 5·1, range 3·2–10·8) which peaked at 24–48 hours. Ten of the patients recovered uneventfully and the %MR returned to normal by day 6. In the one patient who reinfarcted on day 4 (as diagnosed by chest pain, electrocardiographic changes, and a further rise in CK-MB activity), there was a further rise in %MR on day 5. There was no significant correlation between peak CK-MB activity and %MR.

These results provide the first in vivo evidence in human beings of free radical production after myocardial infarction. The time course of these changes suggests that the release of free radicals follows reperfusion of damaged myocardium rather than their instantaneous formation at the time of infarction.

Ambulatory ST segment deviation after acute myocardial infarction: implications for exercise ischaemia and left ventricular function

P Currie, S Saltissi
Department of Cardiology, Royal Liverpool Hospital, Liverpool

To evaluate transient myocardial ischaemia during daily activities in patients recovering from acute myocardial infarction (MI), we performed ambulatory ST segment monitoring both early (mean 6·3 days after MI; n = 166) and late (mean 38 days; n = 145). The findings were correlated with exercise testing (n = 145) and radionuclide left ventricular (LV) function (n = 110). On early monitoring, transient ST segment deviation occurred in 43/166 patients (26%) and was associated with a tendency to reduced LV ejection fraction (mean (SD) 48·4 (11·5)% *v* 52·7 (12·5)%) ($p < 0·07$) and earlier onset of exercise induced ST deviation (mean (SD); 183 (103) s *v* 232 (123) s) ($p < 0·06$). Late ST deviation was detected in 48/145 patients (33%) and was significantly associated with earlier onset of exercise induced ST change 172 (97) s *v* 249 (117) s) ($p < 0·01$), a greater magnitude of maximum ST deviation on exercise (2·2 (1·0) mm *v* 1·6 (0·5)) ($p < 0·01$), and an increased number of ECG leads showing ST deviation on exercise (3·8 (2·3) leads *v* 2·4 (1·5)) ($p < 0·01$). Late ST deviation was not, however, correlated with impaired LV ejection fraction (50·5 (11·3)% *v* 52·3 (12·9)%) (NS).

In this study, transient ischaemia early after MI was associated with a greater impairment of LV systolic function, whereas later ST deviation was a marker for more extensive exercise induced myocardial ischaemia. These findings may have implications both for prognosis and in identifying candidates for coronary revascularisation after MI.

Management of patients after myocardial infarction: Do exercise testing and a more intensive approach make any difference?

J E Sanderson, E Whiteley, K Neubauer
Cardiology Department, Taunton and Somerset Hospital, Taunton

There is a considerable difference between physicians in their management policy for patients after myocardial infarction. To determine whether this affects outcome, we studied the long term prognosis of two groups of patients admitted to a coronary care unit (CCU) with myocardial infarctions in whom management after infarction was different. During 1984–86, 234 patients aged < 70 with proven myocardial infarctions (history, ECG, and enzymes) were admitted into CCU under the care of a physician with an interest in cardiology (121, group A) and a general physician (113, group B). Data were available after a mean follow up of 30 months (range 12–47) in 86 (71%) of group A and 79 (70%) of group B patients. All patients in group A had a pre-discharge limited (stage II Bruce protocol) exercise test (and 71% had a full exercise test at about one month after discharge) and more intensive treatment as a consequence. None of the patients in group B had a pre-discharge exercise test and they were generally discharged to their general practitioner after one outpatient visit. At follow up after 12–47 months, 70% in group A and 52% in group B were well, without any problems. Twenty per cent in group A and 34% in group B (difference χ^2 test $p < 0{\cdot}05$) had angina, heart failure, or a further infarction. Mortality was 10% in group A and 14% in group B. Ten patients in group A and one in group B had coronary artery bypass grafting. These results show that exercise testing and more intensive management after myocardial infarction do make a significant difference to morbidity and possibly to mortality.

Adenosine and angina pectoris

F Crea, G Pupita, A R Galassi, H El-Tamimi,
J C Kaski, G Davies, A Maseri
Cardiovascular Unit, Hammersmith Hospital,
London

Because the intravenous infusion of adenosine (Ad) provokes angina-like chest pain in healthy volunteers, it has been proposed that endogenous Ad, released during myocardial ischaemia, could be responsible for the anginal pain. However, chest pain caused by intravenous Ad could originate from organs other than the heart. To establish its origin, an intracoronary infusion of Ad at increasing concentrations (10^{-5}, 10^{-4}, 10^{-3}, $2{\cdot}5 \times 10^{-3}$ and 4×10^{-3} mol/l) was given to nine patients with stable angina. In the same patients Ad was then infused into the right atrium by the same protocol, but at concentrations 20 times greater. During intracoronary administration of Ad all nine had chest pain similar to their anginal pain: two at a dose 10^{-3} mol/l, four at $2{\cdot}5 \times 10^{-3}$ mol/l, and three at 4×10^{-3} mol/l. During infusion of Ad into the right atrium no patient had chest pain up to a concentration 2×10^{-2} mol/l; in all nine patients the concentration of Ad that produced chest pain was at least 20 times greater than that which provoked chest pain during intracoronary infusion. In 10 other patients with stable angina we performed a single blind, placebo controlled, randomised study to assess the effect of the Ad antagonist aminophylline (Am) (7 mg/kg over 10 min) on exercise induced angina. With Am, angina (assessed by a visual analogue scale) was significantly less than with placebo (48 (26) mm *v* 68 (18) mm, $p < 0{\cdot}02$, respectively), despite a similar peak ST depression (1·5 (0·3) mm *v* 1·6 (0·3) mm respectively).

Intracoronary administration of Ad provokes chest pain at doses that do not produce symptoms during infusion into the right atrium, indicating that the pain originates from the heart. Furthermore, blockade of Ad receptors with Am reduces exercise induced angina. These findings suggest that Ad is a stimulus adequate to produce cardiac pain and that it could be, at least partially, responsible for the anginal pain.

Atherosclerotic human coronary vessels preserve a dilator response to substance P in vivo

D C Crossman,* S W Larkin,* M Dashwood,†
G J Davies,* M Yacoub,‡ A Maseri*
*Royal Postgraduate Medical School, †Royal Free Hospital Medical School, ‡National Heart and Lung Institute, London

Human epicardial coronary vessels respond in vivo and in vitro to the endothelium dependent vasodilators acetylcholine (ACh) and substance P (SP). When ACh is infused into vessels diseased by atherosclerosis, however, it causes constriction not dilatation. This is presumed to be the result of endothelial cell dysfunction allowing the muscarinic constriction to be unopposed. SP is believed to have receptors only upon the endothelium and it dilates normal coronary arteries. The response of diseased vessels to SP is unknown. Five patients with ischaemic heart disease underwent diagnostic catheterisation followed by intracoronary SP infusions. Isosorbide dinitrate (ISDN) was then infused at 1 mg/min. Angiograms were performed before any infusions and after each dose. Two of the five patients showed no response to SP while preserving dilatation to ISDN. Three, however, showed dose dependent dilatation with SP (mean (SD) (%) increase from basal at 2·8 pmol/min SP, 6·2 (3·5)%; 5·6 pmol/min SP, 29·3 (10·5)%; 11·2 pmol/min SP, 32 (12·7)%; 22·4 pmol/min SP, 31·3 (12·2)%; ISDN, 36 (19)%). Only the highest dose of SP (22·4 pmol/min) had systemic effects, and these were slight (changes from beginning to end of infusion: heart rate + 4·6 (5·3) beats/min, mean blood pressure − 5·4 (4·2) mm Hg). To confirm the preservation of SP receptors in atherosclerosis, diseased vessels from a transplant recipient were subjected to autoradiography with 50 pmol/l ^{125}I-SP. Displaceable luminal binding was found adjacent to severe atheromatous plaques.

It is concluded that endothelium can still produce dilator response to SP in the presence of atheroma. The "endothelial dysfunction" seen with ACh must reflect a specific muscarinic dysfunction rather than endothelial dysfunction per se.

Abnormal peripheral vascular response in hypertrophic cardiomyopathy in relation to clinical and prognostic features

P J Counihan, M P Frenneaux, Anne O'Donoghue, D Webb, W J McKenna
St George's Hospital Medical School, London

Exercise hypotension is found in approximately one third of patients with hypertrophic cardiomyopathy (HCM). Exercise hypotension in a small selected cohort was associated with abnormal peripheral vasodilatation, suggesting a mechanism for the exercise hypotension. To examine the association of peripheral vasodilatation and exercise induced hypotension, 40 consecutive patients with HCM (aged 14–67, mean 39 years) underwent symptom limited treadmill exercise testing on at least two occasions. Cuff blood pressure was recorded at minute intervals throughout exercise and recovery. Peripheral vascular responses were assessed by forearm plethysmography with a mercury-in-silastic strain gauge. This technique measures changes in forearm blood flow; forearm vascular resistance (FVR) is calculated from the relation of pressure and flow. A mean of five recordings was made at rest and at the peak of symptom limited supine bicycle exercise. For comparison 12 healthy volunteers were similarly studied. Forearm vascular resistance expressed as the percentage of peak versus baseline was 125–318 (median 213%) in controls and 40–494 (median 163%) in HCM (NS). Eighteen patients who had an abnormal erect exercise blood pressure response had a reduced change in forearm vascular resistance during exercise compared with patients with normal exercise blood pressure (40–138, mean 90 (13)% *v* 141–494, mean 232 (120)%, $p < 0·001$). Univariate analysis showed that of 10 clinical, echocardiographic, and arrhythmia findings only a family history of sudden death was more common in those with abnormal plethysmography (7/18 (39%) *v* 3/22 (14%), $p = 0·06$). The finding of abnormal exercise forearm blood flow in patients with exercise hypotension confirms a mechanism of haemodynamic instability. The lack of relation of abnormal forearm blood flow and clinical features is consistent with previous data in patients who die suddenly while the association with a family history of sudden death suggests a potentially important mechanism that may be genetically determined.

Spontaneous coronary spasm in variant angina results from a local coronary hyperreactivity to a generalised constrictor stimulus

J C Kaski, A Maseri, M Vejar, P Halson, F Crea, D Hackett
Cardiovascular Unit, Royal Postgraduate Medical School, Hammersmith Hospital, London

Focal coronary artery spasm in patients with variant angina can be provoked by diverse constrictor stimuli, thus indicating the presence of a local coronary hyperreactivity. To assess whether spasm, when occurring spontaneously, also results from a local coronary hyperreactivity to a generalised constrictor stimulus or from a localised stimulus emerging from the hyperreactive segment, we studied six patients with variant angina who developed focal coronary spasm spontaneously during cardiac catheterisation. Patients had fixed coronary stenoses ranging from 11 to 42%. Changes of coronary luminal diameter were assessed by an automated edge contour detection computer analysis system. During spontaneous coronary spasm the luminal diameter of spastic coronary segments was reduced by 59·5% compared with control, while the calibre of proximal and distal non-spastic coronary segments was reduced by 13·2% and 14·8%, respectively. Ergometrine, given to four patients, consistently provoked focal spasm in the same coronary segments that developed spontaneous spasm. Intracoronary isosorbide dinitrate dilated spastic and non-spastic proximal and distal coronary segments to a similar extent: 20·7%, 18%, and 16·5% respectively. This study shows that spontaneous focal coronary spasm in variant angina results from a local exaggerated coronary constrictor response to generalised stimuli that also affects all other coronary segments by producing only mild coronary constriction.

Spontaneous coronary spasm in variant angina results from a local coronary hypperreactivity to a generalised constrictor stimulus.

Circulating autoantibodies against "myoendocrine" cells in patients with autoimmune polyendocrinopathy and systemic hypertension

Alida Caforio, W J McKenna, E Bonifacio,
R Wagner, R Gill, E Bosi, G F Bottazzo
St George's Hospital Medical School and Middlesex Hospital, London

In autoimmune polyendocrinopathy organ specific autoantibodies are markers of destruction to the target cells and may precede or be associated with clinical evidence of disease. The potential existence of organ specific autoantibodies to myoendocrine cells in patients with multiple endocrine glands affected by autoimmune disease has not been investigated. We tested sera by indirect immunofluorescence (IFL) on human atrium, ventricle, and skeletal muscle from 166 patients with organ specific autoimmune disease affecting at least two endocrine glands, 54 patients with autoimmune thyroid disease, 27 with recent onset insulin dependent diabetes mellitus, and 200 normal blood donors. Organ specific anti-heart autoantibodies were more common in patients with polyendocrine autoimmune disease (28/166, 17%) than in organ specific autoimmune disease confined to one gland (1/80, 1%, $p < 0.001$) or in normal blood donors (7/200, 3·5%, $p < 0.001$). Organ specific anti-heart autoantibodies were always IgG (titre range 1/10–1/40), reacted with the cytoplasm of atrial and to a lesser extent of ventricular myocytes, and were absorbed with human atrium but not with rat liver or human skeletal muscle homogenates. On univariate analysis cardiac specific autoantibodies were not associated with a particular autoimmune disease or with any other organ specific autoantibody. Positive sera were tested by double IFL with rabbit anti-atrial natriuretic factor (ANF) serum. Both organ specific anti-heart autoantibodies and anti-ANF serum reacted with the cytoplasm of the same atrial cells. Organ-specific anti-heart autoantibodies were associated with a higher frequency systemic hypertension (7/38 (18%) *v* 2/80 (2·5%), $p < 0.008$) and family history of hypertension (12/35, (34%) *v* 5/67 (7%), $p < 0.002$).

These studies in patients with autoimmune polyendocrinopathy show the presence of organ specific cardiac autoantibodies against ANF secreting "myoendocrine" cells in association with the finding of systemic hypertension.

Fibreoptic disposable catheter tip pressure transducer of very small dimensions for cardiovascular investigations

G L Pappageorgio, V J Redding, N B Jones
Department of Biomedical Engineering, University of Leicester, Groby Road Hospital, Leicester

Pressure measurements with fluid filled catheter systems may introduce pressure signal distortion due to the limited and sometimes spurious frequency response of the system. A single-fibre catheter tip pressure transducer has been developed, which overcomes these problems. Low manufacturing cost renders the device disposable after single use. The frequency response is flat up to several hundreds of cycles per second and is determined by the electronic circuitry. The inherent frequency response is much higher. Resolution can be as low as 30 μm of mercury. The external diameter of the smallest available catheter is 0·4 mm (1·3 F) and further miniaturisation is possible. The device has been used for on the bench experiments as well as for arterial and venous pressure monitoring in animals and in human subjects. In view of its small dimensions and the high signal fidelity, the device can be used for direct intracoronary blood pressure monitoring. Immunity to electromagnetic interference, absence of electrical potential within the cardiac cavities, and unlimited catheter length are additional advantages.

Free radical activity in chronic heart failure and effect of captopril

J McMurray, Medula Chopra, J McLay, N Scott,
A Bridges, Jill Belch
Departments of Clinical Pharmacology, Medicine, and Cardiology, Ninewells Hospital, Dundee

Free radicals (FR) are potentially cytotoxic chemical species. There has been much recent interest in the possible role of FR in myocardial reperfusion injury. Coronary artery disease, haemodynamic derangement, and neuroendocrine activation could also promote FR formation in chronic heart failure (CHF). Thus FR generation in CHF might contribute to the genesis and progression of the syndrome. We therefore measured FR activity in 25 patients with stable diuretic treated CHF (New York Heart Association class II-IV) and, for comparison, in 14 age and sex matched controls. We also investigated the potential FR scavenging action of captopril in vitro and in vivo in CHF. Malondialdehyde (MDA), a marker of lipid peroxidation, was used as a measure of FR activity. Patients with CHF had higher MDA concentrations (median 14·7 (IQR 13·3–16·3),) than controls (median 7·8 (IQR 7·3–8·4) ($p < 0·001$). In vitro captopril showed dose dependent FR scavenging activity (where the percentage inhibition of the assay represents general FR scavenging activity): 13·3 (2 0)% (captopril concentration 50 ng/ml), 18·6 (1·3)% (100 ng/ml), and 34·3 (1·6)% (250 ng/ml). In vivo, captopril (dose 6·25–25 mg) caused a small but significant fall in MDA concentration from 14·7 (IQR 13·3–16·3) to 13·1 (IQR 11·4–14·3) one hour after the dose ($p < 0·01$).

These results show that chronic heart failure is associated with increased free radical activity. We confirmed previous reports that captopril has free radical scavenging activity in vitro and showed this effect for the first time in vivo in human beings. This effect of captopril may be of benefit in chronic heart failure.

Hypoxia, myocardial ischaemia, and arrhythmias during sleep in chronic heart failure

S W Davies, J A Wedzicha, L M E John, R Balcon, D P Lipkin
London Chest Hospital, and Royal Free Hospital, London

In severe chronic heart failure (CHF) there is a high incidence of sudden death, attributed to ventricular arrhythmias. In patients with chronic airflow limitation there is a relation between nocturnal episodes of arterial oxygen desaturation and subsequent mortality, but there are no reports of CHF patients. Overnight studies were performed in 10 unselected patients with severe CHF (New York Heart Association grades III-IV) and no evidence of pulmonary disease. Continuous recordings were made of transcutaneous po_2 and pco_2, oxygen saturation (Sao_2) by pulse oximetry, and ECG rate, rhythm, and ST segment shift. During sleep there was a significant fall in mean Sao_2 from 95·1 (1·6)% awake to 92·7 (1 4)% asleep ($p < 0·001$); minimum Sao_2 asleep was 85·1 (2·7)%. During the night Sao_2 was below 95% for 62 (32)% of the time, below 90% for 6 (5) of the time, and below 85% for 1 (1)% of the time. Mean pco_2 rose from 32·1 (9·3) mm Hg awake to 35·9 (10·8) mm Hg asleep ($p < 0·005$). In four patients there were dips (defined as an abrupt fall in Sao_2 of $\geqslant 4\%$ from a stable baseline, lasting $\geqslant 30$ s) with concurrent increases in pco_2. In two patients there was transient bradycardia during the dips; in two there were frequent ventricular extrasystoles during the dips, and in one of these there was significant ST depression ($\geqslant 0·1$ mV at 80 s after J point) during a dip. In the remaining patients occasional ventricular extrasystoles were unrelated to changes in Sao_2.

In severe CHF there were significant episodes of oxygen desaturation during sleep, some of which were associated with arrhythmias or ST segment depression on both. Such episodes might be related to the increased risk of sudden death in severe CHF.

Increase in plasma concentration of atrial natriuretic factor by atriopeptidase inhibition in heart failure: effects on diastolic function

D B Northridge, I N Findlay, S G Dilly, H J Dargie
Department of Cardiology, Western Infirmary, Glasgow and Pfizer Central Research, Sandwich, Kent

Atrial natriuretic factor (ANF) is degraded in man by a neutral endopeptidase (atriopeptidase) located in the kidneys. UK 69 578 is a novel inhibitor of atriopeptidase that raises plasma concentrations of ANF in animals and normal volunteers, resulting in a diuresis and natriuresis. We examined the short term effects of UK 69 578 in six men (mean age 52 years) with mild heart failure (peak oxygen consumption during treadmill exercise 20 4 (range 16–25) ml/min/kg). All medications including diuretics were withdrawn and patients received UK 69 578 and placebo in random order on consecutive days. UK 69 578 caused a threefold increase in plasma ANF accompanied by a diuresis and a rise in mean sodium excretion from 4·9 to 8·8 mmol/h ($p < 0 05$). There was no change in heart rate, arterial blood pressure, or cardiac output. Right atrial pressure fell from 6·7 to 4·7 mm Hg and pulmonary artery wedge pressure fell from 9·2 to 6·7 mm Hg after UK 69 578. The fall in cardiac filling pressures could have been due to either a fall in venous return or an improvement in left ventricular relaxation. Doppler echocardiographic measurements of transmitral blood flow were therefore made to monitor left ventricular diastolic function. There was a fall in peak early left ventricular filling rate from 39·5 to 34 cm/s ($p < 0·05$) and a rise in atrial filling from 40 to 42 cm/s (NS) after

UK 69 578. The ratio of early to atrial ventricular filling rate (E:A ratio), a Doppler index of left ventricular diastolic function, fell from 1·04 to 0·87 ($p < 0·05$).

UK 69 578 caused an increase in plasma ANF with an associated diuresis and natriuresis. We found no evidence of an improvement in left ventricular diastolic function, so the fall in cardiac filling pressures was caused by peripheral effects, most probably dilatation of venous capacitance vessels.

Phosphorus magnetic resonance spectroscopy of leg muscle in heart failure

L Arnolda, M Conway, M Dolecki, H Sharif,
P Sleight, J Ledingham, G K Radda, B Rajagopalan
Medical Research Council Biochemical and Clinical Magnetic Resonance Unit, Oxford

Exercise tolerance is reduced in heart failure but bears little relation to the severity of cardiac dysfunction. Recently much attention has focused on chages occurring in skeletal muscle. Phosphocreatine (PCr) depletion and acidification during exertion is greater in the forearm muscle of patients with heart failure (HF) than in controls (C). Similar changes in leg muscle could contribute to exercise intolerance in HF and account for the poor correlation between the severity of cardiac dysfunction and exercise capacity. Phosphorus spectra were collected from the calf muscle of six patients with HF and five controls at rest and during an incremental exercise protocol with interruptions for measurement of blood flow by plethysmography. Resting PCr/PCr + inorganic phosphate (PCr/PCr + Pi) and pH were similar in HF and controls. The maximum load attained was reduced in HF (7·0 (0·8) W *v* 2·8 (0·6) W $p < 0·01$). All subjects completed the first stage of the exercise protocol (1·5 W for 5 min). PCr/PCr + Pi was reduced in HF at this level of exercise (0·82 (0·06) *v* 0·39 (0 08), $p < 0·01$) but pH was not significantly different (6·99 (0·05) *v* 6·83 (0·09)). Both PCr/PCr + Pi (0·48 (0·07) *v* 0·25 (0·06), $p < 0·05$) and pH (6·92 (0·05) *v* 6·72 (0·08) $p < 0·05$) were lower in HF at maximum exercise although workloads were lower than in the controls.

This implies that the changes cannot be explained by muscle atrophy alone. The lower pH caused by greater production of lactate suggests either an abnormality of oxidative phosphorylation or a greater dependence on anaerobic glycolysis. Blood flow and recovery were not significantly different in HF and controls. These metabolic changes are qualitatively similar but more severe than the changes described in forearm muscle in HF.

Skeletal muscle and whole body protein turnover in cardiac failure

W L Morrison, M C Petch, C Scrimgeour,
M J Rennie
Cardiac Unit, Papworth Hospital, Papworth Everard, Cambridge, and Department of Physiology, University of Dundee, Dundee

Muscle protein wasting commonly accompanies severe heart failure. The mechanism of this so-called cardiac cachexia was investigated in eight patients who showed an average decrease of body weight of 19%, and their results were compared with those from 11 healthy controls. Exchanges of tyrosine and 3-methylhistidine across leg tissue were used as specific indicators of net protein balance and myofibrillar protein breakdown respectively. Whole body protein turnover was measured by a stable isotope labelling technique with L − [1 − ^{13}C] leucine as tracer. In patients with cardiac cachexia there were increases, relative to values in normal control subjects, in leg efflux of tyroxine (− 8·2 (0·6) *v* − 4·2 (0·3) nmol/100 ml leg tissue/min ($p < 0·01$)) and of 3-methylhistidine (− 0·82 (0·10) *v* − 0·14 (0·02) nmol/100 ml/min ($p < 0·005$) (mean (SEM)). The results suggest that in patients with cardiac cachexia the state of net negative protein balance across leg tissue is associated with an increased rate of myofibrillar muscle protein breakdown. The results for whole body protein turnover showed that in cardiac cachexia, compared with controls, there was a depression in leucine plasma flux (79 (8) *v* 133 (6) μmol/kg/h ($p < 0·001$)), leucine oxidation (25 (7) *v* 40 (2) μmol/kg/h ($p < 0 001$)), and protein synthesis (54 (2) *v* 89 (4) μmol/kg/h ($p < 0·001$)).

These results suggest that although there is an overall depression of whole body protein turnover in cardiac cachexia, this is associated with an increase in myofibrillar protein breakdown from skeletal muscle in the leg.

Prospective, randomised, double blind, placebo controlled trial of low dose amiodarone in patients with severe heart failure and frequent ventricular extrasystoles

R A Stewart, W J McKenna, J D Poloniecki,
J K Michelson, S K Das, F Morady, M A Schork,
B Pitt, J M Nicklas
Hammersmith Hospital and St George's Hospital, London; and University Hospitals, Ann Arbor, Michigan, USA

Sudden cardiac death is a common cause of mortality in patients with severe impairment of left ventricular function. To determine whether antiarrhythmic treatment could improve survival in this population, 102 patients were randomly assigned to treatment with amiodarone or placebo in a prospective, double blind multicentre trial. Inclusion criteria were an ejection fraction of < 30%, New York Heart Association class III or IV symptoms, and Lown class II-IV ventricular extrasystoles during 24 hour ECG monitoring. Forty nine patients were randomised to treatment with low dose amiodarone (400 mg/day for four weeks followed by a 200 mg/day maintenance dose) and 53 to placebo. Mean follow up was 383 (38) days. Serious side effects were not seem. Four patients withdrew because of side effects; one from each group because of abnormal liver function tests and two from the amiodarone group because of tremor. Overall mortality and the incidence of sudden death were similar in the amiodarone and placebo treated groups: 14 *v* 12 and 12 *v* 9 patients. Mortality at six and 12 months was 16 *v* 10% and 28 *v* 19% respectively. There was no statistical difference in survival curves for the two groups; the 95% confidence interval for the effect of amiodarone on one year mortality was −11% to +28%. Patients who survived had a shorter preceding duration of symptomatic failure than those who died (26 (4) *v* 53 (10) months, p = 0·004), but a similar ejection fraction (20 (1)% *v* 19 (1)%) and baseline arrhythmia findings and electrolytes. A change in the incidence of ventricular arrhythmia was not related to outcome.

This pilot study suggests that amiodarone 200 mg/day can be safely administered to patients with impaired left ventricular function, but that at this dose level there was no effect on mortality or the incidence of sudden death.

The relations of serum cholesterol, blood pressure, and smoking habit to coronary heart disease in a population with low mean concentrations of serum cholesterol

Z Chen, R Collins, R Peto, S MacMahon, W Li
Clinical Trial Service Unit, University of Oxford

The relations of serum cholesterol, systolic blood pressure (SBP), and cigarette smoking to the risk of fatal coronary heart disease (CHD) were investigated in data from two prospective observational studies of 9021 Chinese men and women (aged 35–65 at baseline) living in urban Shanghai. The mean values (SD) of serum cholesterol and SBP at baseline were 4·2 mmol/l (0·93) and 127 mm Hg (22), and 5·0 mmol/l (0·83) and 123 mm Hg (22) in the two cohorts; while for cigarette smoking the proportions of current regular smokers were 40% and 46% respectively. Forty three CHD deaths (7% of the total deaths) were recorded over 8–13 years of follow up. Survival analysis of the combined data from both cohorts showed that serum cholesterol and SBP were significant predictors of CHD death (z = 3·34 and z = 4·44 respectively, both 2P < 0·001), that persisted after taking into account other risk factors. The relations were independently statistically significant in each of the cohorts and in both men and women. The association between cigarette smoking and risk of CHD was also positive, though not significant. It is estimated from the combined data that 10% differences in baseline serum cholesterol (0·47 mmol/l) and SBP (12·5 mm Hg) were associated with 23% (6) and 35% (7) differences respectively in the risk of CHD death. Both cholesterol concentrations and SBP measured at *baseline* are not perfectly correlated with *usual* long term values. Remeasurements of the cholesterol and SBP some years after baseline in the first cohort indicated that a difference of 10% baseline cholesterol and SBP corresponds to a difference of only 4% and 6% in long term *usual* cholesterol and SBP respectively. This suggests that differences of about 4% and 6% in *usual* cholesterol and in *usual* SBP might correspond to 23% (6) and 35% (7) differences in CHD risk respectively.

These results show clearly that even in a population with a low cholesterol and a low risk of CHD, serum cholesterol and blood pressure are still important determinants of the subsequent risk of CHD death.

Cholesterol management algorithms and British serum cholesterol concentrations: implications of the Scottish Heart Health and MONICA Studies

H Tunstall-Pedoe, W C S Smith, R Tavendale
Cardiovascular Epidemiology Unit, University of Dundee, Dundee

The Scottish Heart Health and Scottish MONICA studies have produced highly standardised measurements of serum total cholesterol based on large representative samples of men and women (total 10 450) aged 25–64 years living in different parts of

Scotland. The findings should be typical of Britain as a whole and are presented in such a manner that it is possible to read off the proportion of the population with a reading at or above any specific value. Overall concentrations are high but there is considerable variation by age and sex, particularly in middle age where there is a rise in men and a much larger rise in women. Recently published management algorithms use cutting points of 5·2 mmol/l, 6·5 mmol/l, and 7·8 mmol/l (200 mg/dl, 250 mg/dl, 300 mg/dl), or of 6·2 mmol/l (240 mg/dl) to determine specific actions. These would generate an unsupportable case load (much larger than that implied by the United States population data from which they were derived) that would be dominated by older women. High cholesterol values (above 7·8 mmol/l) are so common in Scots when they reach 45 years of age that they cannot be attributed to familial hypercholesterolaemia in 98% of cases.

Policy for coronary prevention in Britain must take account of these high cholesterol concentrations. High risk algorithms that implicate the bulk of the population in extra diagnostic tests should be adjusted to the local situation; dietary advice should be more widely generalised.

Cardiac noradrenaline output during percutaneous transluminal coronary angioplasty

A J McCance, J C Forfar
Department of Cardiology, John Radcliffe Hospital, Oxford

Percutaneous transluminal coronary angioplasty (PTCA) is a useful model for studying the effects of short periods of coronary occlusion and reperfusion. Coronary venous and arterial noradrenaline (NA) concentrations were measured during PTCA in 14 patients. Whole body NA kinetics were also measured, and in five patients coronary sinus blood flow was measured. In patients undergoing left anterior descending (LAD) PTCA ($n = 8$) great cardiac vein NA was 157 (38) pg/ml before the first balloon inflation, 194 (45) pg/ml 60 seconds after balloon inflation ($p = 0·11$), and 295 (94) pg/ml during early reperfusion ($p < 0·05$). The response of great cardiac vein NA to coronary occlusion and reperfusion was highly variable, some patients showing no change and one an eightfold increase during early reperfusion. No changes in coronary sinus NA were seen during PTCA ($n = 6$) of the right or circumflex coronary arteries. Aterial NA and whole body NA spillover to arterial plasma rose during the period of LAD PTCA from 120 (28) pg/ml to 150 (32) pg/ml ($p < 0·01$) and from 299 (52) ng/min to 383 (63) ng/min ($p < 0·01$) respectively. Coronary occlusion was associated with a reproducible decline in coronary blood flow to 75–90% of the pre-occlusion flow and reperfusion was associated with the rapid development of reactive hyperaemia (125–150% of pre-occlusion flow). Cardiac NA extraction was reduced during reperfusion. A semiquantitative assessment of cardiac NA spillover during LAD PTCA suggested that cardiac NA spillover increased nearly threefold during early reperfusion, but was unchanged during coronary occlusion.

Thus during LAD PTCA there is evidence of a minor increase in overall sympathetic tone and a variable but sometimes dramatic increase in great cardiac vein NA, especially during reperfusion. Enhanced NA release at this time may predispose to reperfusion injury and arrhythmias.

Can epoprostenol (prostacyclin) infusion during coronary angioplasty prevent adverse changes in platelet function?

A H Gershlick, Denise Syndercombe-Court,
A D Timmis, M T Rothman, C Layton R Balcon
London Chest Hospital, London

Restenosis after angioplasty remains an unresolved problem, limiting the value of the procedure. Indirect evidence suggests platelets may play a central role, through their enhanced interaction with the balloon damaged vessel wall. Antiplatelet agents, such as aspirin have not reduced the incidence of restenosis. As part of a study assessing the effect of intravenous epoprostenol (prostacyclin (PGI_2)) on restenosis, we have evaluated the effect of this compound on the changes in transcardiac platelet function induced by angioplasty. Patients were randomly allocated to PGI_2 (4 ng/kg/min) or placebo infusion, started before angioplasty. The platelet activation index (PAI), a sensitive measure of platelet hyperaggregability, was measured in samples taken from the aortic root and coronary sinus before angioplasty (A1 and C1 respectively) and in samples from the same sites after angioplasty (A2 and C2 respectively) in both control and treatment groups. For the placebo group ($n = 14$) values of PAI were significantly higher in C2 11·9 (6·5) (mean (SD)) than that in A1 7 7 (4·9) ($p = 0$ 006), A2 8·6 (3·2) ($p = 0·01$), and C1 7·7 (3·4) ($p = 0·0002$). Similarly for the PGI_2 infusion group ($N = 10$) C2 values (11·1 (4·3)) were significantly greater than A1 (7·8 (3·1)) ($p = 0$ 008), A2 (6·3 (2·8)) ($p = 0·006$), and C1

(6·8 (3·7)) ($p = 0.002$). There were no significant differences between the two groups in each of A1, A2, C1, and C2.

This study confirms that coronary angioplasty results in platelet hyperaggregability, which may predispose to restenosis. PGI_2 does not influence these changes in platelet function and it is likely, therefore, that this compound will not reduce the incidence of restenosis.

Epidural spinal stimulation in patients with intractable angina

J E Sanderson, T D Waterhouse, R B G Palmer
Cardiology Department, Taunton and Somerset Hospital, Taunton

Epidural spinal cord stimulation (ESCS) is a recognised technique for the treatment of severe peripheral vascular disease and it has been established that it relieves pain and increases blood flow. However, it has not been used to any extent in patients with angina. Recently we implanted ESCS units in seven patients with intractable angina (mean age 61 (range 47 to 72 years)). Six patients had had coronary artery bypass surgery (× 2 in two patients and × 3 in one patient), one was inoperable, and all were on full medical treatment. Under local anaesthetic a stimulating electrode (Medtronic Sigma) was inplanted in the epidural space at the level of T1–T2, positioned to produce parasthesia across the chest and into the left arm (that is the area of angina pain), and connected to the stimulator (Medtronic Itrel) implanted in the axilla. There were no complications with implantation. Postoperatively all patients noted a considerable improvement in symptoms: consumption of glyceryl trinitrate capsules was reduced from average 8·5/day (4–20) before operation to nil in five patients and average of 3/day in two patients after operation. Treadmill exercise time increased from 8·3 (2·4) min to 9·24 (2·2) min, and total ST segment depression at peak exercise fell from 5·6 (3·9) mins to 3·6 (2·6) mins. Onset of angina during right atrial pacing increased from 128 (19) to 144 (19) beats/min. However, the reduction in ischaemic ECG changes was small and did not always correlate with symptomatic relief.

ESCS seems to relieve angina but it is not clear whether this is entirely through reduction in ischaemia—other pain relieving mechanisms may be involved.

Influence of lipid abnormalities on the development of coronary arterial disease after cardiac transplantation

M Barbir, N R Banner, C J Reid, G R Thompson,*
A G Mitchell, M H Yacoub
Harefield Hospital and *Hammersmith Hospital

Coronary artery disease (CAD) in the cardiac allograft is emerging as the most serious long term complication of cardiac transplantation. The cumulative risk of developing angiographic CAD in patients treated with conventional immunosuppression with prednisone and azathioprine (15% at one year ($n = 17$), 34% at two years ($n = 11$), and 76% at three years ($n = 5$)) was higher than in those treated with cyclosporin and azathioprine without routine oral steroids (6·4% at one year ($n = 294$), 10% at two years ($n = 87$), and 14·3% at three years ($n = 128$)) ($p < 0.001$)). Serum lipid concentrations were higher at one year in the conventional immunosuppression group than in the cyclosporin group (mean (SD) total cholesterol (TC) 8 (SD) 1·98 mmol/l *v* 6·1 (1·66) mmol/l, $p < 0.001$; and mean triglyceride (TG) 2·6 (1·8) mmol/l *v* 1·4 (1·9) mmol/l, $p < 0.001$). The relation of serum lipid concentrations to the subsequent development of CAD was investigated in 95 consecutive patients with angiographically normal coronary arteries one year after transplantation. The cumulative incidence of CAD in those with the TC > 5·8 mmol was 9·3% at two years ($n = 39$), 24·4% at three years ($n = 20$), and 45% at four years ($n = 8$) compared with 4·3% at two years ($n = 44$), 7·4% at three years ($n = 31$), and 14% at four years ($n = 14$) in those with a TC < 5·8 mmol/l ($p < 0.05$). Similarly the incidence of CAD was increased in patients with higher triglycerides.

Hyperlipidaemia seems to be an important risk factor for the development of CAD after cardiac transplantation.

The epicardial approach to surgical treatment of Wolff-Parkinson-White syndrome

C P Ratnatunga, E S Barin, D W Davies,
A W Nathan, S J Edmondson
St Bartholomew's Hospital

The epicardial approach for ablation of accessory pathways (AP) in Wolff-Parkinson-Whitesyndrome was proposed to allow surgery on the closed heart. Unlike the endocardial approach, no aortic cross clamping or cardioplegic arrest is necessary—and occasionally cardiopulmonary bypass is not required. We report our experience of the epicardial approach in 28 patients with 34 AP (mean age 31·2 years (range 15–53 years) 13 men). Presenting arrhythmias were atrioventricular reentrant tachycardia alone (AVRT) (six patients), AVRT with atrial fibrillation (AF) (18), AVRT with AV nodal tachycardia (two), and AF or atrial flutter alone (two). The principal indication for surgery was rapid atrioventrivular conduction associated with the risk of atrial fibrillation (20 patients). Other indications were: refractoriness or intolerance to medications (four patients) and patient preference for surgical cure (4). Symptom duration ranged from 1·5 to 50 years. One patient had associated scimitar syndrome and three had Ebstein's anomaly. There were no deaths or significant morbidity. Thirty two of 34 AP were abolished, including all 15 left free wall pathways and 15/16 posteroseptal ones. Reoperation was required in two patients (one right free wall and one multiple pathways). No late symptomatic recurrences occurred after a mean follow up of 16 months.

Our experience shows that the epicardial approach is a safe and effective alternative to the conventional endocardial method.

Deleterious effects of prostaglandin E1 in 12 hour lung preservation

R S Bonser, L S Fragomeni, S W Jamieson, M P Kaye
London Chest Hospital and University of Minnesota, Minnesota, USA

The effects of preharvest infusions of PGE_1 into the pulmonary artery on hypothermic pulmonary preservation were evaluated in 12 dogs undergoing double lung transplantation. Animals received grafts stored for 12 hours at 4°C after pulmonary artery flush with 60 ml/kg 4°C Collins solution. Six donor animals received a PGE_1 infusion (20–120 mg/kg/min) for 20 minutes before and during harvest. After implantation recipients were maintained on a fixed fractional inspiratory oxygen (Fio_2) (0·4) and cardiopulmonary function was studied for 20 hours. Treatment with PGE_1 resulted in reduced survival ($p < 0·05$) and an increased alveolar-arterial oxygen gradient ($p < 0·05$) 30 minutes after reperfusion. After 60 minutes of reperfusion mean arterial Po_2 (Fio_2 0·4) was 148 mm Hg in controls and 80·5 mm Hg in the PGE_1 group ($p < 0·02$). There was no significant difference in pulmonary vascular resistance, oxygen saturation, airway resistance, compliance, and physiological dead space between groups at any time after implantation but these indices had deteriorated when compared with donor animals. After 20 hours of reperfusion po_2 (Fio_2 0·4) in the control group was 140 (52) mm Hg. The method of preservation in control animals resulted in good survival and adequate gas exchange.

Donor pretreatment with PGE_1 did not improve lung preservation and it seemed to have deleterious effects on early graft function.

Microemboli and cerebral impairment during cardiac surgery

W Pugsley, L Klinger, C Pascalis, M Harrison, S Newman, T Treasure
The Middlesex Hospital and the Middlesex and University College Medical Schools, London

Transcranial Doppler can be used to detect microembolic events (MEE) during cardiac surgery. We used this technique in a prospective randomised study on 100 patients who underwent coronary artery surgery. Patients were randomised to bypass (Bubble Oxygenator, Harvey H1700) with or without arterial line filtration (40 Micron, Pall EC Plus). Change from preoperative neuropsychological performance was assessed at eight days and eight weeks by a battery of ten tests. Perfusion technique was standardised and continuously monitored. The electroencephalogram (CFAM, Medaid) was recorded. We used transcranial Doppler (TC2–64, EME) to measure MEE. There was no significant difference in age between the patients with arterial line filtration (mean (SD) 56·6 (6·1) years) and those without (mean 54·2 (8·5). Bypass times and prebypass $Paco_2$ were also similar for both groups. MEE (1–25) occurred in all patients during aortic cannulation and at the inception of bypass (5–100). On bypass patients with arterial line filtration had significantly ($p < 0·01$) fewer MEE (0–10 per 30 minutes) than those without (30– >250 per 30 minutes). No MEE were seen at the end of bypass. The patients who had had arterial line filtration performed better on short term memory tests ($p < 0·01$, Wilcoxon) at eight weeks and were less depressed than those who did not.

We identified high risk periods for MEE during CPB and showed that microemboli contribute to the cerebral impairment seen after cardiac surgery.

Distension during surgical preparation reduces short term patency in a pig model of arteriovenous bypass grafting

A J Bryan, G D Angelini, H M J Williams,
A C Newby
Department of Cardiology, University of Wales College of Medicine, Heath Park, Cardiff

It has been suggested that early occlusion of coronary and peripheral arteriovenous bypass grafts may occur as a result of platelet activation caused by endothelial denudation during surgical preparation. This has not, however, been demonstrated directly. Using a pig model, we studied the effect of surgical preparation with or without distension for one minute at 23°C with iso-osmotic sodium chloride solution on endothelial coverage, platelet adhesion, and early patency in autologous saphenous vein to common carotid artery bypass grafts. Pigs (25–30 kg) were heparinised by intravenous bolus (1 mg/kg) and grafts 2–3 cm in length were made by an end to end anastomotic technique. After two hours of arterial implantation grafts were fixed by in situ perfusion with buffer containing 2·5% (v/v) glutaraldehyde. Endothelial coverage and platelet adhesion were then measured by scanning electron microscopy. Graft patency was evaluated in a separate series of pigs by reoperation at 1–4 weeks. Grafts made with undistended vein removed after two hours of arterial implantation had 98 (1)% ($n = 6$) endothelial coverage, with platelet adhesion confined to small areas of endothelial loss. Grafts made with distended vein had 38 (14)% ($n = 6$) endothelial coverage ($p < 0{\cdot}001$ *v* undistended) and showed extensive platelet adhesion to denuded subendothelium, with fibrin deposition and mural thrombi in two of the grafts. Graft patency at 1–4 weeks was 96% with undistended vein and 63% with distended vein ($n = 25$ each, $p < 0{\cdot}005$).

The data show directly that distension leads to endothelial damage and platelet activation and that this is associated with reduced early patency.

Cardiac transplantation in patients with present or past malignant neoplasms

D Aravot, N Banner, A Khaghani,
Melissa Fitzgerald, F Musumeci,
Rosemary Radley-Smith, M H Yacoub
Harefield Hospital, Harefield, Middlesex

Between January 1980 and December 1988, 640 patients have undergone cardiac transplantation at Harefield Hospital. Ten of these patients had cancer—eight were "cured" before transplantation of systemic malignancy and two were transplanted for primary neoplasm of the heart. Seven patients had cardiomyopathy induced by doxorubilicum (adriamycin) and one by radiotherapy given two months to 13 years previously. The total dosage of adriamycin ranged from 300 to 450 mg/m^2. The original neoplastic diseases were: histiocytosis (one), neuroblastoma (one), rhabdomyosarcoma (two), osteosarcoma (one), non-Hodgkin lymphoma (two), and Hodgkin lymphoma (one). Two patients have undergone cardiac transplantation for primary malignant tumours of the heart: one patient had neurofibrosarcoma of the right ventricle and another had leomyosarcoma of the left atrium. There were three early deaths (within the first month after transplantation, all in the adriamycin group). The remaining patients are well with no evidence of residual disease or recurrence, during a period of follow up ranging from four months to five years. All patients received our usual immunosuppressive regimen (cyclosporin and azathioprine).

Cardiac transplantation is a practical treatment for selected patients with primary cardiac malignancy or cardiac failure complicating the successful treatment of systemic malignancy, despite the need for continuous immunosuppression.

Medium term cardiovascular effects of implantable left ventricular assist devices (LVADs) in the calf

P S Withington, T R Graham, M Marrinan,
D G White, P Colvin, C T Lewis
The London Hospital, Whitechapel and Royal Veterinary College, Hatfield

Implantable left ventricular assist devices (LVAD) are currently used as mechanical bridges to cardiac transplantation and have been proposed for long term use in patients unsuitable for or denied a transplant. We report the haemodynamic results of use of an implantable pusher plate LVAD that uses cannulation of the left ventricular apex of the heart in four 72·7 kg (mean) 13 week old (mean) calves. Systolic blood pressure, diastolic blood pressure, central venous pressure, pulmonary artery pressure, pulmonary artery wedge pressure, total blood flow, LVAD blood flow, and heart rate were measured before and after LVAD implantation, and two weeks and seven weeks after insertion. There was an immediate deterioration in native left ventricular (LV) function after insertion with a satisfactory output maintained by the LVAD. At two weeks the native LV had apparently returned to normal, with the overall cardiac output increasing by 40·3% because of the LVAD contribution. At seven weeks there was a significant increase in both systolic and diastolic blood pressures, the mean (SD) values being 125·5 (19·6) to 165 (29·4) mm Hg (p = < 0·05) systolic and 63·5 (25) to 97 (22·4) mm Hg (p = < 0·05) diastolic. There was a significant increase in heart rate from a mean of 85 (13·6) before operation to 109 (24·3) beats/min seven weeks after operation.

LVADs provide adequate haemodynamic support (as confirmed by the increased cardiac output) while maintaining a low pulmonary capillary wedge pressure. The observed hypertension seven weeks after implantation requires further evaluation and elucidation of its cause as this may have important implications for the long term use of these devices.

Comprehensive validation of the Cardioscint: a system for continuous monitoring of left ventricular function

P Broadhurst, P Cashman, P Dasgupta, A Lahiri, E B Raftery
Northwick Park Hospital, Harrow, Middlesex

A new, miniature (diameter 45 mm) non-imaging nuclear probe (Cardioscint) has been developed, enabling continuous monitoring of left ventricular (LV) function and, from an averaged ECG, the ST segment level. The device was validated in 36 patients (23 men and 13 women) undergoing routine gamma camera radionuclide ventriculography. Positioning the probe under the camera produced a mean (SD) difference in LV ejection fraction (EF) between camera and probe of 3·8 (9·6)% when a manually selected paraventricular background region of interest was used, and 1·5 (8·6)% when automatically estimated background (= 75% of end diastolic counts) was used. In only two patients was an adequate LV time-activity curve not obtainable. Accuracy was maintained in female patients and in cases with severe wall motion abnormality. In seven patients with obstructive coronary artery disease undergoing atrial pacing, all developed angina, associated with a mean peak rise in pulmonary capillary wedge pressure (measured by Swan-Ganz catheter) of 9 (range 1–22) mm Hg and an ST segment change of 0·9 (range 0·1–1·7) mm. When LV function was assessed with the probe it showed a mean fall in stroke counts of 46 (range 29–56)% and EF of 43 (range 17–68)%, relative to values at rest.

The probe thus provides a reliable estimation of EF and is able to track rapid changes in LV volumes and function that occur in myocardial ischaemia induced by atrial pacing. Further exploration of the clinical usefulness of the Cardioscint is clearly warranted.

Whole bolus ratio: a new technique for assessing valvar regurgitation from first pass radionuclide angiography

M N Wiseman, L J Dyke, D S Dymond
St Bartholomew's Hospital, London

First pass radionuclide assessment of valvar regurgitation (VR) has centred on stroke count ratios, with summed right ventricular stroke counts as a reference for left ventricular stroke counts. This technique has obvious shortcomings where there is appreciable tricuspid regurgitation or poor right ventricular function. A bolus injected through a central venous catheter gives a frame early in the study where the whole bolus is within the field of view. The counts in this frame may be taken as the whole bolus and valvar regurgitation can be assessed from the whole bolus ratio (WBR), defined as (sum of left ventricular stroke counts: whole bolus). In 15 control patients studied in the anteroposterior (AP) and 30° right anterior oblique (RAO) projections WBRs were 0·52 (0·05) (AP) and 0·51 (0·08) (RAO) (p = NS). In the same patients the stroke count ratios were 0·8 (0·1) (AP) and 0·9 (0·25) (RAO) (p = NS). In 20 patients with left sided valvar regurgitation WBR in both AP and RAO projections correlated closely with CO/(LV minute volume) at cardiac catheterisation (AP—r = 0·70, p < 0·01; RAO—r = 0·90, p < 0·001). Repeat nuclear studies in 16 VR patients 50 (45) days later used peripheral venous injections. Stroke count ratios in valve patients at first and second study correlated in the RAO (n = 9, r = 0·76, p < 0·025), but not in the AP projection (n = 13, r = 0·29, p = NS), whereas WBR showed good correlation over time in both projections (AP—n = 13, r = 0·62, p < 0·025; RAO—n = 9, r = 0·88, p < 0·01). The WBR method provides a useful method of determining the severity of left sided valvar regurgitation without reference to the right ventricle and a reproducible technique by which long term changes in severity may be followed.

The place of aortography and computed tomographic scanning in the investigation of suspected acute thoracic aortic dissection

J M Morgan, H H Gray, P J Oldershaw
Brompton Hospital, London

Historically aortography (AO) has been regarded as the standard investigation for acute aortic dissection (AAD). Between 1978 and 1982 24 patients were referred with suspected AAD and all had AO, the results of which were either confirmed at operation (n = 12) or necropsy (n = 2), or supported by clinical outcome (n = 8). One patient with an equivocal aortogram, however, had a type III AAD at necropsy. One patient was lost to follow up. From 1983 to 1988 computed tomographic scanning (CT) has also been available and has been used alone in 33 patients with suspected AAD. A further 22 patients had AO alone during the same period. Three of these 55 patients were lost to follow up but in none of the remainder (n = 52) was misdiagnosis apparent as judged by operative findings (n = 19), necropsy (n = 2), or clinical outcome (n = 31). An additional 15 patients required both investigations because clinically inadequate information had been obtained from the first. In 10 the results of AO and CT were concordant but in five they were discordant. In three of these five patients AO failed to show a dissection but subsequent CT showed type III (n = 2) or type II (n = 1) AAD and in two AO showed type I dissections that had not been seen on the CT scan.

When used alone both AO and CT will misdiagnose occasionally. Aortography seems to miss types II and III AAD and CT scanning tends to miss type I—missing type I dissections has potentially more serious clinical consequences.

Pulsed Doppler assessment of left ventricular diastolic function in acute myocardial infarction

D J Flannery, B D Devlin, N P S Campbell
Regional Medical Cardiology Centre, Royal Victoria Hospital, Belfast

To investigate the factors that influence left ventricular (LV) diastolic filling in acute myocardial infarction (MI) 75 patients had cross sectional and Doppler echocardiographic studies from the LV outflow tract (to measure stroke index), LV inflow tract (to measure the contribution of atrial contraction to LV filling), and left atrium (to look for mitral regurgitation), with measurement of radionuclide left and right ventricular ejection fraction (LV and RVEF)—all at a mean of 48 hours after the onset of MI. Advanced age, reduced stroke index, and increased echocardiographic infarct size were associated with an increase in the atrial contribution to LV filling, with a concomitant reduction in early passive filling, suggesting that these factors were associated with impaired LV myocardial relaxation. Multiple regression analysis, however, showed that mitral regurgitation, although only mild in most patients, had a stronger influence on LV filling dynamics and produced the opposite effect—increasing the passive contribution and decreasing the atrial contribution to LV diastolic filling. LV filling was not independently influenced by factors such as LV or RVEF, pulmonary venous congestion, or pericardial effusion.

The occurrence of mild degrees of mitral regurgitation in acute MI makes the effects of MI on Doppler indices of intrinsic myocardial relaxation.

Are haemodynamic changes during ventricular tachycardia useful in treatment?

D W Davies, E S Barin, C Y Wong, R D Levy, A W Nathan
St Bartholomew's Hospital, London

Implantable devices capable of both defibrillation and pacing to terminate ventricular arrhythmias (VA) are now available with defibrillation, which ideally is reserved for arrhythmias with haemodynamic (BP) deterioration. Intracavity right ventricular (RV) impedance changes can detect deterioration during VA. Most patients with VA and coronary heart disease (CHD) have more LV than RV dysfunction so that indices of RV performance during VA may underestimate changes in systemic BP. Pulmonary artery (PA) and systemic BP were monitored during control rhythm (eight sinus, two paced) and VA in 10 patients (eight with CHD, two with cardiomyopathy (CM)) during electrophysiological study. Control heart rates ranged from 60 to 115 (mean 77) beats/min. Twelve VAs were induced, rates ranging from 160 to 200 (mean 182) beats/min. Control systemic systolic BP ranged from 105 to 150 (mean 128) mm Hg falling in all at onset of VA, with BP ranging from 35 to 120 mm Hg. Systemic BP rose with time in six, fell further in three, and remained stable in one. Phasic BP was lost for the first beats of VA in four patients, with pulsus alternans being seen in three during sustained VA. Control PA systolic BP ranged from 16 to 100 (mean 39) mm Hg. This rose in two, fell in four, and was unchanged in four patients at the onset of VA. Pulmonary BP during VA ranged from 8 to 50 mm Hg, also varied with time, phasic BP being replaced by respiratory swing in both patients with cardiomyopathy.

Haemodynamic monitoring of VA confirms that, in CHD, PA BP changes less than systemic BP with too much variability during VA to be useful diagnostically.

Long term follow up of endocardial pacing in children of 15 kg or less

J A Till, S Jones, E A Shinebourne, D E Ward
Brompton Hospital and St George's Hospital, London

When small children require permanent pacing, the epicardial route is traditionally used because of limited venous access, their small size, and continuing growth. Structural abnormalities add to the difficulties of obtaining and retaining lead position. Since 1983 we have used the transvenous route and have now paced 21 children 15 kg or under (range 2·8 kg to 15 kg, median 7·7 kg), aged between one month and five years three months. Indications for pacing were complete atrioventricular block (CAVB)—congenitalin three and surgically induced in 17. One other child had surgically induced sinuatrial disorder. Two children had dual chamber systems and 19 had ventricular pacing (five rate responsive units). All generators were multiprogrammable and positioned in a pectoral pouch; we used the subclavian vein for lead insertion. A loop of ventricular lead was fashioned in the atrium to allow for growth and seems to have unravelled successfully in all. Tined leads were used in 19 (11 steroid eluting) and screw-in leads in two. Atrial screw-in J electrodes were used in two. Follow up is from four months to five years four months (median two years four months). One child required generator replacement at four years, after predicted battery deletion. Three had minor complications; one requiring repositioning of a lead and another repositioning of a generator shortly after insertion. The third had acute transient poor myocardial function which recovered with no intervention. Three had major complications: one pocket infection and erosion necessitating complete system replacement and two lead fracture.

Endocardial pacing is safe, reliable, and convenient in small children of 15 kg or less, and seems to be preferable to the epicardial approach.

Unmasking of latent pre-excitation: efficacy of adenosine and vagal manoeuvres in sinus rhythm

C J Garratt, A Antoniou, M J Griffith, D E Ward, A J Camm
St George's Hospital Medical School, London

In a minority of patients with accessory atrioventricular connections, ventricular pre-excitation is absent in sinus rhythm but is apparent during atrial arrhythmias, atrial pacing, or manoeuvres that increase conduction time through the atrioventricular node (latent pre-excitation). The aim of the study was to evaluate the efficacy of vagal manoeuvres and intravenous adenosine in unmasking ventricular pre-excitation in a group of 20 patients referred for evaluation of paroxysmal supraventricular tachycardia. None of the patients had electrocardiographic evidence of pre-excitation during sinus rhythm. Left and right carotid sinus massage and Valsalva manoeuvre were performed in a random order twice in each patient. Subsequently intravenous adenosine was given in four incremental doses ranging from 0·05 to 0·20 mg/kg. All patients noticed mild, transient flushing or dyspnoea after adenosine but no serious adverse effects occurred. Intravenous adenosine produced evidence of latent pre-excitation in four patients, one of whom had pre-excitation shown by vagotonic manoeuvres. Electrophysiological study in the four patients with positive responses to adenosine showed ventricular pre-excitation during atrial pacing or atrial extrastimuli in each case. Of the 16 patients with a negative response to adenosine two had evidence of latent pre-excitation at electrophysiological study. The remaining patients with negative responses had accessory pathways that conducted in the retrograde direction only (six patients), dual atrioventricular nodal pathways (six patients), or inducible atrial tachycardia (two patients).

Intravenous adenosine during sinus rhythm showed latent pre-excitation in four of six patients and produced no adverse effects in 20 patients with a history of paroxysmal supraventricular tachycardia. Vagal manoeuvres during sinus rhythm showed latent pre-excitation in one patient only.

Electrophysiological follow up of patients with sinus node disease paced with atrial demand pacemakers

P P Murphy, Patricia Morton, J G Murtagh, M E Scott, D B O'Keeffe
Cardiac Unit, Belfast City Hospital, Belfast

Patients with sinus node disease might be paced in atrial demand (AAI) mode but for the development of atrioventricular conduction disturbances in some. It may be possible to detect those at low risk of conduction disease at pacemaker implantation. Forty two patients with sinus node disease had electrophysiological studies (EPS) at the time of pacemaker implantation. These patients were followed up over a mean of 30 months. Twenty five patients had repeat HV times recorded by non-invasive signal averaging. Mean HV time before pacing was 46·8 ms and on follow up was 46·2 ms (p = NS). Thirty three patients had repeat atrioventricular Wenckebach point (AVW) measurement. AVW was > 120 beats/min in all patients before pacing. After pacing two patients had values of 115 and 105 beats/min. Both patients were on antiarrhythmic drugs for supraventricular arrhythmias, were symptom free, and required no change in pacing mode. One patient developed Mobitz II 2:1 block six months after pacing requiring change of pacing mode. This patient had an abnormal surface ECG at the time of pacing.

Combined use of surface ECG and EPS can identify a group of patients with sinus node disease at low risk of development of conduction tissue disease who can safely be paced in AAI mode. Even in the presence of normal EPS an abnormal surface ECG should be an indication for implantation of a ventricular lead.

Transoesophageal approach to defibrillation of ventricular fibrillation

P McKeown, S Croal, J D Allen, J Anderson,
M M Khan, A A J Adgey
Department of Physiology, Queen's University,
Bioengineering Centre, University of Ulster, and
Regional Medical Cardiology Centre, Royal Victoria
Hospital, Belfast

In anaesthetised greyhounds weighing 18–32 kg, a unipolar oesophageal electrode with four isolated electrodes on polyvinylchloride (PVC) tubing was positioned maximally behind the left atrium. The external electrode was a steel paddle (diameter 8·1 cm) placed over the left apex. Ventricular fibrillation (VF) was induced and terminated via the oesophagus in 10/11 dogs. Energies used for successful termination of VF ranged from 25 to 65 J (mean 38·90 J) (stored). A stable system for use in patients was then designed, consisting of four separate electrodes, each of coiled gold plated copper wire, mounted on PVC tubing. We have previously reported successful cardioversion of atrial arrhythmias using this system. Such a system was electively positioned in five patients undergoing electrophysiological studies. Two of the individual electrodes are used to obtain a bipolar oesophageal ECG and the other two for energy delivery, should a sustained haemodynamically important arrhythmia requiring countershock develop. In four patients no significant arrhythmia was inducible. VF was induced in the other patient—a 65 year old woman (weight 69 kg) with documented coronary artery disease and pre-hospital VF. Successful transoesophageal ventricular defibrillation was effected with minimal delay by a single shock of 50 J delivered energy. The predicted transoesophageal impedance in this patient was 57 Ω, considerably lower than the predicted transthoracic impedance of 77 Ω. Oesophagoscopy was performed 96 h after defibrillation and showed no evidence of electrode or current induced damage.

We believe that this is the first reported case of transoesophageal ventricular defibrillation of VF in a human being and we think that this technique represents a considerable advance in defibrillation and may lead to the development of a pocket sized defibrillator.

Initiation and termination windows in tachycardia: reproducible in the long term?

C Bucknall, N Sulke, S Karani, E Sowton
Guy's Hospital, London

A new microprocessor driven antitachycardia (AT) bipolar pacemaker (PM) has been developed for patients with reciprocating tachycardia. It has a non-invasive electrophysiological (EP) facility, Holter memory, and unique self learning algorithm. Patients underwent preimplantation EP studies to determine the nature of the tachycardia and its initiation (IW) and termination windows (TW). After implantation the AT system was telemetered from a computer to the PM. Non-invasive EP assessments of IW and TW for each tachycardia were performed repeatedly with the patient lying and standing via the microprocessor interface to closely simulate spontaneous attacks. The adaptive table system allowed the pacemaker to learn the most effective TW and continually update itself. Follow up at one, three, and six months of the first three patients with paroxysmal re-entry supraventricular tachycardia showed consistently rapid termination of their attacks. In patients with two different tachycardia rates the pacemaker learnt two independent termination sequences. Non-invasive electrophysiological study at follow up showed minor changes in IW in one patient, but the IW remained constant in the others. Termination windows for each tachycardia were unchanged in all patients. Telemetered data allowed rapid assessment of the date, time, rate, and successful TW for each attack. These telemetered sequences confirmed the reproducible nature of TWs.

Minor changes occurred in the sequences required for tachycardia initiation; termination windows were highly reproducible in patients with re-entry supraventricular tachycardia.

Clinical assessment of rate adaptive paging by the ventricular depolarisation gradient as the control parameter in a closed loop system

V E Paul, C J Garratt, D E Ward, A J Camm
Department of Cardiological Sciences, St George's Hospital, London

The opposing effects of exercise/stress and rate on the ventricular depolarisation gradient facilitate closed loop, rate adaptive pacing in the Prism pacemaker. The rate response to exercise and other stimuli has been assessed. Between September and November 1988 10 patients (eight men) with chronotropic incompetence received Prism pacemakers. One month after implantation all patients underwent treadmill testing and one minute of maximal (burst) activity. During activity and recovery the ECG was continually monitored and the times to achieve initial rate response, 50% maximum rate, and maximum rate were recorded. The pacing response to mental stress, isometric activity, and postural changes were also recorded. In all patients both graded and burst activity resulted in a prompt rate response with initial increases occurring within 10 seconds. There was no difference in response times between the two activities (mean 5 s for burst activity and 5·9 s for graded activity) but the time to maximum heart rate was significantly less during burst activity (mean 79 s) than during graded activity (136 s). Mental activity/stress increased pacing rate by an average of 17 beats/min while isometric exercise increased the rate by a mean of 23 beats/min. Postural changes produced a paradoxical response with a rate increase (mean 31 beats/min) on tilting from erect to supine; tilting from supine to erect had no effect.

The prism rate adaptive pacemaker provides prompt and reliable rate response to exercise and to most non-exercise stimuli.

Observations on tissue changes and arcing with multiple high voltage low energy shocks for electrode catheter mediated cardiac ablation

E S Barin, P C Macpherson, Siew Y Ho,
S A Waterfield, A P Armstrong, A W Nathan
St Bartholomew's Hospital, and National Heart and Lung Institute, London

The use of high voltage short duration pulses at low energy may overcome the problems experienced with direct current cardiac ablation at higher energies. We studied the tissue effects of multiple short duration shocks at high voltage and the effect of intervals between pulses in freshly excised porcine hearts in saline and blood media. A custom designed high power pulse generator delivering high voltage, exponentially decaying DC shocks of 20 μs duration was used. Unipolar endocardial shocks were delivered via a 7F USCI electrode catheter. The effects of increasing pulse energy (0·1–0·7 J), number (1–128), or the interval between pulses (120–4000 μs) were examined separately. Visible arcing occurred with increasing total energies, but only when the intervals between pulses were < 300 μs, at outputs up to 3 kV (30 A). Tissue effects also increased with total energy while varying with pulse interval. Paradoxical increases in myocyte changes occurred at peak energies when the interval between each pulse was increased from 120 to 4000 μs (without arcing). Transition from normal to abnormal tissue was discrete with no carbonisation.

This study suggests that the pulsing intervals when high voltage multiple shocks are used affects tissue in a paradoxical fashion, possibly related to arcing phenomena. The histological and electrophysiological effects of this form of low energy electrical ablation warrant further investigation to define their role in catheter mediated ablation.

The influence of pacing rate on QT shortening with exercise

J G Coghlan, B Madden, M S Norell, C Ilsley,
A G Mitchell
Harefield Hospital, Harefield, Middlesex

The QT interval shortens with increasing heart rate and exercise. It has been suggested that up to 50%

of the exercise induced shortening is independent of the increase in heart rate, but this "rate independent" effect has only been studied at resting heart rates. We studied 11 patients (age 38–64) with complete heart block who had been fitted with rate programmable ventricular pacemakers. They were paced at varying rates (70–130 mm) at rest and then performed symptom limited treadmill testing at both low (70–95 mm) and high (120–130 mm) pacing rates. The QT interval was measured from the pacing artefact to the apex of the T wave at a paper speed of 50 mm/s. Pacing at rest from 70–120 yielded an average QT shortening of 17% (mean (SD) 341 (24·5) ms to 283 (15·1) ms; p < 0·0001). The initial QT response to exercise was an increase in the QT interval by 0·8% in the first minute, followed by a reduction in the QT interval. Symptom limited exercise (mean seven minutes) at low and high rates both resulted in an average QT interval reduction of 4% (355 to 346 ms at low rate, 280 to 269 ms at high rate). Correlation analysis of the QT response to exercise both at high and low pacing rates gives an r value of 0·96 (p < 0·0001). This confirms that the rate independent QT response is constant even at high rates. Furthermore, the reduction in QT interval induced by exercise is considerably less than previously suggested.

Results of percutaneous balloon dilatation for critical aortic stenosis in neonates with severe endocardial fibroelastosis

E J Ladusans, J M Parsons, S A Qureshi, E J Baker, M J Tynan
Department of Paediatric Cardiology, Guy's Hospital, London

Balloon dilatation (BD) was attempted in six neonates with critical aortic stenosis (CAS). In three patients CAS was detected on fetal ultrasound. The left ventricle (LV) was dilated and poorly contracting in these patients, with mean LV internal end diastolic diameter (LVID) of 1·8 cm, and was severely hypoplastic in the remaining three (LVID mean 0·57 cm). All patients had echocardiographic features of severe endocardial fibroelastosis (EFE). Mean age at intervention was 3·1 days (range 0·4–12) and mean weight 3·0 kg (range 2 2–3·7). BD was not possible in three patients. In two the balloon catheter could not be advanced beyond the aorto-iliac junction; both patients sustained femoral artery disruption and died shortly after the procedure. In one patient the balloon catheter could not be advanced across the aortic valve and surgical valvotomy was performed. The patient died four hours after operation. BD was accomplished successfuly in three patients. The mean balloon to annulus ratio was 1·1 (0·19); the transvalvar pressure gradient fell from 50 (20 to 20 (17) mm Hg. Aortic regurgitation was mild in two and moderate in one after the procedure. There were no arterial complications in these patients. In all three there was persisting severe left ventricular dysfunction despite adequate relief of obstruction. All three died a mean of 12·3 days (range 10–17) after balloon dilatation; severe EFE was confirmed at necropsy.

Balloon dilatation in neonates with critical aortic stenosis and severe endocardial fibroelastasis was associated with a high risk that was independent of left ventricular size. Even after successful valve dilatation the prognosis was poor.

Reversion of atrial fibrillation: intravenous flecainide versus intravenous disopyramide

M N Wiseman, A W Nathan
St Bartholomew's Hospital, London

Drug reversion of atrial fibrillation (AF) to sinus rhythm avoids the need for direct current cardioversion under general anaesthesia. In this study we compared intravenous disopyramide (D) with intravenous flecainide acetate (F) in 25 patients with spontaneous AF. Subjects were allocated randomly to double blind treatment with D (12 patients) or F (13 patients), maximum dose 2 mg/kg over 10 minutes, although the infusion was stopped if reversion occurred. Preceding duration of AF was 132 (223) days (F patients 141 (269) days, D patients 124 (200) days, p = NS). Seven patients treated with F reverted compared with only one treated with D (p < 0·05). All patients who reverted had AF present for ⩽ 26 h, and when those patients who had had AF for ⩽ 2 days were reviewed there was no significant difference in the rates of reversion (F 7/8, D 1/3). In two patients in each group adverse events were recorded: one F patient reported a slight headache, another developed ventricular bigeminy in the two minutes after reversion; one D patient developed a few short runs of ventricular tachycardia after injection, and another had the injection terminated after eight minutes with the onset of ventricular tachycardia (> 15 beats). DC cardioversion was immediately performed in 15 patients who had not reverted, and was successful in all cases.

Flecainide is an effective and safe agent in the reversion of acute AF; patients who have had AF for ⩽ 2 days may be candidates for drug reversion; patients who have had AF for > 2 days should be considered for elective DC cardioversion, although there may be a role for pretreatment with an intravenous antiarrhythmic.

Comparison of silent ischaemia after infarction and in chronic stable angina: effect of diltiazem

B Khan, M de Belder, J D Skehan, P G Mills
The London Hospital, London

With 72 hour ambulatory electrocardiographic (ECG) monitoring to detect and measure silent, symptomatic, and total ischaemia we investigated 40 patients with angiographically documented coronary disease and positive results or exercise testing. A randomised double blind placebo controlled protocol was used to assess the effect of diltiazem. Twenty one patients had had a myocardial infarction (group I) and 19 had stable angina with no previous infarction (group II). There was no difference in age, sex, risk factor profile, or extent of coronary disease between the two groups. None of the patients showed resting ST segment abnormalities. Patients had 1440 hours of ambulatory ECG monitoring while taking placebo and 1408 hours while taking diltiazem. In group II there was little effect of diltiazem on either the total number of episodes (14 with placebo *v* 12 with diltiazem) or the number of silent ischaemic episodes (9 with placebo *v* 8 with diltiazem). In group I there was a reduction in the frequency of total ischaemic episodes (7 episodes with placebo *v* 4 with diltiazem) and silent ischaemic episodes (7 with placebo *v* 4 with diltiazem).

Diltiazem reduces the frequency of both total ischaemic episodes and silent ischaemic episodes in patients with previous myocardial infarction. This effect was not seen in patients with stable angina and no previous myocardial infarction.

Assessment of mitral prostheses with transoesophageal echocardiography

P Nihoyannopoulos, D Kambouroglou,
A Nadazdin, J Joshi, P Ghosh, C M Oakley
Royal Postgraduate Medical School, Hammersmith Hospital, London

The usefulness of transthoracic colour Doppler echocardiography (TTE) in evaluating artificial valve function is limited because of flow masking by the prosthetic material. Transoesophageal echocardiography (TOE) offers a superior echocardiographic window for assessing valvar or paravalvar leaks. To determine the value of TOE in assessing mitral prostheses we studied 18 patients with clinically suspected prosthetic valve malfunction using both TTE and TOE. All TOE studies were performed without complications and were well tolerated even in very sick patients. Prosthetic valve regurgitation was assessed as mild, moderate, or severe according to the jet area occupying the left atrium. Nine out of 18 patients were found to have mild (5) or moderate (4) mitral regurgitation on TTE. On TOE prosthetic valve regurgitation was clearly seen in 17 of the 18 patients; the regurgitation was considered to be mild in eight, moderate in three, and severe in six. In one patient in whom mild regurgitation was suspected on TTE, TOE failed to show any leak. Six patients had their mitral prosthesis replaced (five with dehisced valves, one endocarditis). The remaining 12 patients continued to be followed medically as the paraprosthetic leaks were at the most only moderate. There were no stenotic or thrombosed prostheses in the series.

TOE is a more accurate and sensitive method than TTE for evaluating mitral prosthesis. It is highly specific not only in confirming clinical suspicion but also in excluding prosthetic valve malfunction.

Do reciprocal electrocardiographic changes in acute Q wave myocardial infarction represent additional ischaemia or necrosis?

D Jain, A Lahiri, U Raval, T Smith, E B Raftery
Northwick Park Hospital, Harrow, Middlesex

The underlying pathophysiology of reciprocal electrocardiographic(ECG) changes in acute myocardial infarction is unclear. ^{111}In-antimyosin (In-AM), resting ^{201}Tl (Tl) and gated blood pool imaging were performed in 37 consecutive patients with first Q wave acute myocardial infarction. In 27 patients reciprocal ECG changes were present (group 1) and in 10 they were absent (group 2). The myocardial segments representing the reciprocal ECG leads were compared in the two groups for uptake of In-AM, Tl defects, and wall motion abnormalities. No significant differences were detected between the segments with or without reciprocal changes. Abnormalities in the myocardial segments representing reciprocal leads in groups 1 and 2 were as follows: wall motion abnormalities were present in eight (33%) *v* three (30%); In-AM uptake in 10 (37%) *v* three (30%); Tl defects in two (7%) *v* two (20%); wall motion abnormalities alone in four (15%) *v* one (10%); no abnormalities in the reciprocal segment in 12 (44%) *v* six (60%). Multivessel coronary disease and ejection fraction values were also similar in both groups.

Thus in patients with acute myocardial infarction the presence of reciprocal ECG changes does not necessarily imply myocardial necrosis or ischaemia in the myocardial segments associated with the ECG changes.

Long term survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia

W J McKenna, Katherine M Adams, J D Poloniecki, Shaughan Dickie, Celia M Oakley, D M Krikler, J F Goodwin
Hammersmith and St George's Hospitals, London

In hypertrophic cardiomyopathy the detection of non-sustained ventricular tachycardia during electrocardiographic (ECG) monitoring is associated with a sevenfold increase in mortality from sudden death. In two well matched consecutive groups with ventricular tachycardia the use of amiodarone when compared with that of conventional class 1 agents was associated with improved short term survival. Since 1982 our policy has been to perform 24–48 hour ECG monitoring yearly and to treat patients with non-sustained ventricular tachycardia with the lowest effective dose of amiodarone. We report survival in 38 consecutive patients who received amiodarone as initial treatment after non-sustained ventricular tachycardia was detected. Patients received amiodarone 400–1600 mg, median 800 mg, daily for one week followed by a maintenance dose of 100–400 mg, median 200 mg, daily with mean plasma concentrations of amiodarone and desethylamiodarone of 1·1 (0·4) and 1·0 (0·5) mg/l. Two additional patients did not tolerate amiodarone; they received nadolol and propafenone and survived. Forty patients who received amiodarone for other indications (including supraventricular arrhythmias and severe symptoms) were excluded; their survival has been previously reported. Five year survival in the 38 patients with ventricular tachycardia who received amiodarone was compared with that in 104 patients without ventricular tachycardia who did not receive amiodarone. Kaplan-Meier survival estimates for mortality related to disease were 94% and 84%, respectively, with a confidence interval for the difference of − 1% to 22%. For sudden death five year survival was 100% and 91%, respectively ($p = 0·19$).

The use of low dose amiodarone in consecutive patients with ventricular tachycardia who were at increased risk of sudden death resulted in a lower incidence of sudden death and of mortality related to disease than was observed in low risk patients who did not receive amiodarone. This confirms that the beneficial effect of amiodarone on mortality in patients with hypertrophic cardiomyopathy and ventricular tachycardia is maintained long term.

Percutaneous balloon dilatation may relieve pulmonary venous pathway obstruction after Mustard's operation for transposition of the great arteries

I D Sullivan, S G Cooper. Catherine Bull, J F N Taylor
Hospital for Sick Children, London

Mortality at reoperation for pulmonary venous pathway obstruction after Mustard's operation for transposition of the great arteries is more than 20%. Consequently, during 1988 we attempted percutaneous balloon dilatation in three patients with mid-baffle pulmonary venous pathway obstruction. Balloon catheters were introduced retrogradely across the site of obstruction through the tricuspid valve. The procedure was unsuccessful in a three year old boy. Evidence for relief of obstruction in the other two patients, who were 8 and 14 years old, were angiographic findings of improved calibre where the pulmonary venous pathway narrowed and improvement in the Doppler spectral signal at this site from an obstructed to a normal pattern, together with symptomatic improvement. Balloon dilatation was performed twice in one of these patients. The improvement seen with Doppler and the symptomatic improvement were sustained in both patients three months after balloon dilatation.

This technique may offer effective relief of pulmonary venous pathway obstruction in some patients with this potentially lethal complication of Mustard's operation.

Baroreceptor sensitivity in patients after infarction: correlation with electrophysiological studies

T G Farrell, T C Cripps, V Paul, A J Camm
Department of Cardiological Sciences, St George's Hospital Medical School, London

Depressed sensitivity of the baroreflex in patients after infarction has been reported as a risk factor for sudden death. Such patients may be prone to life threatening ventricular arrhythmias as a consequence of disordered autonomic tone. To investigate this possibility we compared baroreceptor sensitivity in 40 patients (mean age 56·3 (10·6) years) seven to 10 days after infarction with programmed ventricular stimulation. Baroreceptor sensitivity was studied with an infusion of phenylephrine and expressed as the slope of the regression line relating change in blood pressure to RR intervals (ms/mm Hg). Programmed ventricular stimulation elicited sustained monomorphic ventricular tachycardia (SMVT) in six patients, ventricular tachycardia (PMVT) in 13, and no arrhythmia in 21. Three patients who later developed clinical ventricular tachycardia had inducible SMVT at the time of the study. There was a significant difference in baroreceptor sensitivity between patients with SMVT and those with PMVT (2·1 (1·5) *v* 5·8 (3·8); $p = 0·032$) and between patients with SMVT and those in whom no arrhythmia could be induced (2·08 (1·51) *v* 7·71 (3·75); $p = 0·003$). Within the SMVT group it was impossible to differentiate those who later developed clinical ventricular tachycardia by baroreceptor sensitivity. The sensitivity was directly related to ejection fraction ($r = 0·47$, $p < 0·01$), with an inverse relation to age ($r = 0·41$, $p = 0·01$), but there was no significant difference in ejection fraction between the patients with SMVT and those with no arrhythmia or programmed ventricular stimulation. One way analysis of variance showed a significant difference in baroreceptor sensitivity between the three groups (SMVT, PMVT, and none ($p < 0·006$).

Baroreceptor sensitivity testing identified patients at risk of ventricular arrhythmias after myocardial infarction and gave similar results to programmed ventricular stimulation. It also confirmed earlier suggestions that abnormal autonomic tone in patients after infarction predisposes to ventricular arrhythmias and sudden death.

Autonomic regulation of pre-excitation induced by respiration

G S Butrous, G Kaye, A J Camm
St George's Hospital Medical School, London

Six patients who had intermittent pre-excitation that was induced at peak inspiration and disappeared on expiration were studied (age 26–54 years). The anterograde refractory period of the accessory pathway was 300–540 ms). Pre-excitation appeared during phase IV of the Valsalva manoeuvre (parasympathetic predominant phase) in all patients but not during phase II (sympathetic predominent phase). The appearance of pre-excitation was not related to changes in RR intervals (control 637 (106) ms; phase II 552 (112) ms, phase IV 792 (115) ms) or AH interval (control 80 (17) ms, phase II 70 (19) ms, phase IV 69 (19) ms). Application of a vacuum neck collar (pure parasympathetic stimulation) did not induce pre-excitation despite changes in the RR interval similar to those seen during phase IV of the Valsalva manoeuvre. After atropine (0·04 mg/kg) or propranolol (0·2 mg/kg), or both, pre-excitation could not be induced by respiration or the Valsalva manoeuvre, whereas isoprenaline (3 μg/min) provoked persistent pre-excitation in two of the six patients.

These results suggest that autonomic tone has a direct role in regulating pre-excitation that is not associated with the changes in RR and AH intervals. Pre-excitation appeared during parasympathetic stimulation that was preceded by an increase in sympathetic tone—for example, the Valsalva manoeuvre or respiration—but not after isolated sympathetic or parasympathetic stimulation. This suggests that the development of pre-excitation is determined by sympathetic-parasympathetic interaction.

Electrophysiological basis of the configurations of the ventricular paced evoked response

M W Baig, J C Cowan, J Cant, E J Perrins
Leeds General Infirmary, Leeds

The comparative effects of local and global electrophysiological events that contribute to the configuration of the paced evoked response are unknown. The time courses of paced evoked responses and simultaneously recorded monophasic action potentials have been compared, although separate electrodes were used for recording the electrograms. The interval to 90% repolarisation of the monophasic action potential coincided with the apex of the evoked T wave and it was suggested that local electrical events were the dominant contributors to the configuration of the paced evoked response. The interelectrode distances and hence the areas of the heart that lie under the dipoles of these two electrograms are, however, different, and as the paced evoked response is a unipolar signal it is more logical to conclude that it reflects generalised ventricular electrophysiological events, although evidence for this has hitherto been lacking. We recorded the unipolar paced evoked responses generated between the tip and ring electrodes of bipolar leads and a common remote indifferent electrode in 10 patients. Subtraction of the digitised electrograms yielded the signal recorded between the tip and ring electrodes. In each case this residual signal showed a pacing artefact followed immediately by a negative deflection, which was the depolarisation wavefront. Thereafter the signal remained isoelectric.

These results suggest that the configuration of the paced evoked response is determined by far field and not local electrical phenomena.

Significance of frontal plane axis in non-ischaemic right ventricular tachycardias: echocardiographic and histological evaluation

D Mehta, H Odawara, W J McKenna, M J Davies, A J Camm
St George's Hospital Medical School, London

Right ventricular cardiomyopathy is increasingly recognised as a cause of arrhythmic death in young people. We assessed the value of echocardiography compared with endomyocardial biopsy in identifying right ventricular disease. Right ventricular biopsy and detailed echocardiographic evaluation of the right ventricle were performed in 27 patients (mean age 40, range 19–56 years) with ventricular tachycardia of proved right ventricular origin. Only patients with normal chest radiographs, left ventricular function, and coronary arteriograms were included. At least three endomyocardial biopsy specimens were obtained from the right ventricle. The dimensions of the right ventricle were measured by echocardiography at multiple levels at the inflow tract, body, and the outflow tract both in short and in long axis views, the measurements being compared with those from normal subjects. Nine patients had abnormal biopsy specimens on light microscopy with findings suggestive of cardiomyopathy or right ventricular dysplasia. Abnormal echocardiographic results, defined as an increase in at least two of the eight dimensions or wall motion abnormalities, or both, were seen in nine patients. There was a strong association between abnormal myocardial histological results and abnormal echocardiographic results ($p < 0.001$). An abnormal echocardiogram was 94% specific and 80% sensitive for abnormal myocardial histological results. The findings on echocardiography and biopsy were correlated with electrocardiographic features of ventricular tachycardia. Evidence of right ventricular disease was seen in all six patients with superior frontal plane axis of clinical ventricular tachycardia compared with four out of 21 patients with inferior axis ($p < 0.001$).

Thus in patients with right ventricular tachycardia abnormal echocardiographic results were specific for myocardial pathology. A superior frontal plane axis of ventricular tachycardia in this group strongly suggested right ventricular disease, whereas an inferior frontal plane axis was often not associated with any morphological or histological abnormality of the right ventricle.

Reproducibility of non-ischaemic right ventricular tachycardias induced by exercise

D Mehta, D E Ward, A J Camm
St George's Hospital Medical School, London

Exercise testing is often undertaken for therapeutic assessment of patients with non-ischaemic right ventricular tachycardia, especially when the tachycardia is not inducible by programmed electrical stimulation. Thus the consistency of inducing ventricular tachycardia or successive exercise tests is essential. To establish the consistency of exercise testing in provoking ventricular tachycardia 10 patients (mean age 36 years) who had ventricular tachycardia during treadmill exercise test were subjected to a second exercise test 24–48 hours later. All patients had had ventricular tachycardias documented and had normal coronary arteriograms. The clinical tachycardia was sustained in four patients (> 30 s) and not sustained in six. Treadmill tests were performed 72 hours after stopping all antiarrhythmic treatment; none of the patients was taking amiodarone. The tests were performed with the standard Bruce protocol and continuous monitoring of three electrocardiographic leads. The timing of all arrhythmic events and the events were recorded during both tests. The sinus rate just before the onset of tachycardia was also recorded. In eight of the 10 patients ventricular tachycardia was reproduced at the second test; in each case the tachycardia was similar in rate, duration, and configuration to that during the initial test. In both patients who did not have ventricular tachycardia during the second test sustained tachycardias had been induced at the first. The sinus rate at the onset of ventricular tachycardia during the second test was within 10 beats/minute in six of the eight patients in whom consistent exercise induced tachycardia had been reproduced.

Thus false conclusions of drug effectiveness can be reached in about 20% of cases when exercise testing is used for therapeutic assessment. We suggest two baseline tests to exclude patients with non-reproducible arrhythmias before this method is used to select treatment.

Simplification of the diagnosis of broad complex tachycardia by multivariate analysis

M J Griffith, N J Linker, J Micklewright,
D E Ward, A J Camm
St George's Hospital, London

Previous work on the diagnosis of broad complex tachycardia has concentrated on univariate analysis of either electrocardiographic (ECG) or clinical criteria, resulting in a proliferation of diagnostic rules. The aim of this study was, by using stepwise logistic regression, to explore the relation between ECG and clinical criteria and allow simplification of the diagnosis. Clinical and ECG data were collected from 102 patients with broad complex tachcyardia (QRS width > 110 ms), 69 with ventricular tachycardia, and 33 with supraventricular tachycardia, the diagnosis having been established electrophysiologically. Leads I, aVF, V1, and V6 were dichotomised on the basis of QRS waveforms identified on univariate analysis, separately for right and left bundle branch block pattern, to favour ventricular or supraventricular tachycardia. The shift in the axis from sinus rhythm to tachycardia was dischotomised at a difference of 40°. Clinically a history of myocardial infarction or an abnormal cardiothoracic ratio were significant independent predictors, whereas age, a history of angina, congestive heart failure, collapse during tachycardia, and smoking were not significant. With ECG criteria alone, R or S wave delay in left bundle branch block pattern tachycardia, a shift in the axis of more than 40°, and waveforms in aVF and V1 were significant independent predictors, whereas the width or rate of tachycardia, waveforms in V1 or V6, and tachycardia axis were not significant. With combined ECG and clinical data four variables were significant ($p < 0{\cdot}001$). A history of myocardial infarction had the highest coefficient (6·30); a shift in the axis of more than 40° and the QRS waveforms in aVF and V1 had similar coefficients (4·5, 4·53, and 3·44). Applied retrospectively to the data they achieved a 93% predictive accuracy, which was not increased if other variables were added.

In conclusion only four criteria, a history of myocardial infarction, the QRS waveform in leads V1 and aVF, and a shift in the axis from sinus rhythm to tachycardia of more than 40°, are independent predictors of the diagnosis of broad complex tachycardias, with a predictive accuracy of 93%.

Pre-excitation induced by exercise: association with anteroseptal accessory atrioventricular connections that are sensitive to adenosine and verapamil

C J Garratt, M J Griffith, G S Butrous, D E Ward,
A J Camm
St George's Hospital Medical School, London

Pre-excitation induced by exercise is an unusual phenomenon. We report on four patients in whom ventricular pre-excitation was reliably induced by exercise (three male, one female, mean age 18 years). All patients had frequent palpitation that was resistant to conventional medical treatment. Initiation of orthodromic re-entrant tachycardia occurred in the exercise recovery phase in all patients. All patients had single accessory connections located in the anteroseptal position (located by intraoperative epicardial mapping in two and by transvenous endocardial mapping in all four). Anterograde effective refractory periods of these pathways were 430 ms, 340 ms, 340 ms, and 330 ms at a pacing rate of 100 beats/minute. The corresponding retrograde effective refractory periods were 230 ms, 210 ms, 260 ms, and 310 ms, respectively. No patient had long RP′ tachycardia. None of the pathways had features of Mahaim fibre conduction. Intravenous adenosine given during tachycardia (three patients) reproducibly terminated the arrhythmia in the anterograde limb, with spontaneous reinitiation of tachycardia occurring within 1–3 s. Two patients underwent successful operation by the conventional endocardial route; the two remaining patients were studied further. In these patients intravenous adenosine and verapamil abolished pre-excitation during exercise, adenosine being associated with the initiation of tachycardia. Vagotonic manoeuvres (release phase of the Valsalva manoeuvre) also reproducibly abolished pre-excitation.

All four patients with pre-excitation induced by exercise had accessory connections in the anteroseptal position. In two patients these connections were shown to have properties in common with atrioventricular nodal tissue because anterograde conduction was blocked by adenosine, verapamil, and vagotonic manoeuvres.

Paced and natural rate response during everyday activity

N Sulke, A Pipilis, S Karani, C Bucknall, E Sowton
Guy's Hospital, London

The heart rate of 50 patients with pacemakers who were aged 17–78 years was compared with that of 20 controls matched for age (23–76 years) during everyday activities, including climbing and descending stairs; lifting suitcases; intermittent, slow, and fast walking; talking while walking; resting mental stress; changing posture; and exercise during a graded treadmill exercise test. Six rate response systems were used: Sensolog in 10, Activitrax in eight, Meta in eight, QT in six, DDD in 10, and activity sensing DDDR in eight. Pacemakers with an activity sensor produced a larger rate response than that seen in controls when the patients descended stairs and lifted suitcases but did not respond to mental stress. The QT and Meta were slow to respond and persisted in high rate response when patients stopped being active. DDD units showed a diminished response when the patients were lifting and talking while walking but otherwise mimicked the response in controls except during maximal treadmill exercise, when upper rate limiting came into effect. The closest response to a normal rate response occurred in DDD and DDDR systems. The QT and Meta responded well to resting stress but slowly to exertion. Sensolog and Activitrax had inappropriate rate responses when the patients lifted the pacemaker arm or descended stairs.

Until a multisensor ventricular rate response system is available combining an activity sensor with a separate physiological sensor dual chamber systems continue to provide the best substitute for sinus node function during everyday activity.

Intravascular three dimensional imaging of arteries: a novel ultrasound system

C J Burrell, R I Kitney, K Straughan,
A H McDonald, M T Rothman
The London and Whitechapel Hospitals and
Imperial College, London

The use of percutaneous angioplasty for peripheral and coronary disease is increasing, and new methods of removal, stenting, or thermal moulding of atheroma are under evaluation. Appropriate use of these options will be facilitated by better imaging of abnormal vessels. Direct fibreoptic visualisation requires replacing blood with non-respiratory translucent fluid. This limitation is overcome by using ultrasound data acquired intraluminally to image the vessel. We have developed a complete ultrasound imaging system for visualising and reconstructing long segments of peripheral and ultimately, coronary arteries. Piezo electric crystals mounted on to a 9F catheter and placed intraluminally send and receive ultrasound signals for real time data acquisition. A computer based system analyses the reflected signals using locally developed software to reconstruct images of the vessel as two dimensional slices (using picture elements, pixels). A series of two dimensional slices form the basis of a three dimensional reconstruction (using volume elements, voxels). Programs allow rotation, slicing, radiographic simulation, edge enhancement, and tissue characterisation of the acquired images.

Images of arterial models and of human in vitro atheromatous arteries have been reconstructed. There is an excellent correlation between the reconstructed images and these "phantoms"; in vivo evaluation is in progress and providing exciting preliminary images.

Response of flow and distribution to stress in normal coronary arteries

Ann C Tweddel, W Martin, I McGhie, I Hutton
University Department of Medical Cardiology,
Royal Infirmary, Glasgow

The outcome after infarction is dependent upon the volume of myocardium at risk; this depends on anatomical dominance, which varies between people. The contribution of each major coronary vessel to flow and volume of myocardium supplied was assessed by clearance of Xeron-133 in nine patients with right dominant arteriographically normal vessels—at rest, during atrial pacing, and immediately after symptom limited exercise. In the distribution of the left anterior descending coronary artery (LAD) flow increased significantly by 13 (14%) and 40 (6)% with atrial pacing at 90 and 110 beats/minute and by 18 (5)% after exercise; and in the circumflex distribution (Cx), by 16 (4)% and 51 (7)% with pacing, and 24 (6)% after exercise. In contrast, in the inferior surface of the left ventricle, supplied by the right coronary artery (RCA), flow was unchanged with atrial pacing (− 4 (2)% and − 4 (2)%) or after exercise (− 18 (5)%). The volume of distribution within the myocardium supplied by each major coronary artery was unchanged: for the LAD it was 50·3 (2·9)% at rest, 51·3 (4·5), 51·6 (2 8)% with atrial pacing and 45·3 (2·9)% after exercise; for the Cx artery it was 52·3 (7·3)% at rest, 48·4 (4·2) and 46 8 (2·2) with atrial pacing, and 51/1 (5·8)% after exercise; and for the RCA it was 39 (9·4)% at rest, 45 2 (4·5) and 45 (7·8)% with atrial pacing, and 42 6 (6·4)% after exercise.

Much of the left ventricle has a dual blood supply particularly the inferoposterior surface and the individual variation in myocardial volume supplied is greatest in the RCA distribution. During stress, increased myocardial flow seems to be provided essentially by the left coronary artery, suggesting a mechanism for the differing effects of anterior and inferior ischaemia on left ventricular function.

Is pulmonary wedge pressure a good index of intraoperative myocardial ischaemia? A correlative electrocardiographic and transoesophageal echocardiographic study

M E R M van Daele, G R Sutherland, M M Mitchell, O Prakash, E N Rulf, J R T C Roelandt
Thoraxcentrum, University Hospital Rotterdam-Dijkzigt, Rotterdam, The Netherlands

Pulmonary wedge pressure is often monitored during operation to assess changes in myocardial function, but its value as an indicator of ischaemia is uncertain. Previous studies have shown an increase in pulmonary wedge pressure during induced ischaemia in cardiac pacing and percutaneous transluminal coronary angioplasty, but it is unclear whether such changes can be extrapolated to the spontaneous ischaemia that may be acquired during the induction of anaesthesia in patients with ischaemic heart disease. We studied 68 patients undergoing anaesthesia for coronary artery bypass graft operations by recording simultaneously the pulmonary wedge pressure, a 12 lead electrocardiogram (ECG), and myocardial wall motion as monitored by transoesophageal echocardiography. Five recordings per patient were made every 10 minutes, before, during, and after induction. In 12 of the 68 patients myocardial ischaemia, defined as a newly acquired regional wall motion abnormality, was detected by transoesophageal echocardiography. Ten of these 12 patients had ⩾ 1 mm concomitant ST depression in the 12 lead ECG. The onset of ischaemia was accompanied by a mean increase in pulmonary wedge pressure of 3·2 (4·9) mm Hg compared with 0·0 (2 2) in the patients who did not develop ischaemia ($p < 0\ 01$). Using an increase in wedge pressure of 3 mm Hg as an indicator for the onset of ischaemia we found a sensitivity of 18% and a positive predictive value of 22%.

The onset of myocardial ischaemia in the group was associated with a small increase in pulmonary wedge pressure, but the wide individual variability in the pressure changes in both patients with ischaemia and patients without ischaemia resulted in many false positive and false negative results when pulmonary wedge pressure was compared with wall motion abnormalities detected by transoesophageal echocardiography in individual patients. In our experience the monitoring of pulmonary wedge pressure is not a valuable method of detecting myocardial ischaemia during anaesthesia.

Pulmonary capillary permeability in chronic left heart failure

S W Davies, J Bailey, J Keegan, D P Lipkin, R Balcon, R Rudd
London Chest Hospital and Royal Free Hospital, London

Patients with severe chronic left heart failure may be comparatively resistant to pulmonary oedema at pulmonary wedge pressures that would cause severe pulmonary oedema in acute left ventricular failure. Decreased pulmonary microvascular permeability has recently been shown in severe rheumatic mitral stenosis, which like chronic left heart failure, is characterised by chronic pulmonary venous hypertension. Pulmonary microvascular permeability was measured in five patients with severe chronic heart failure (New York Heart Association class III-IV) and in 11 controls with normal left ventricular function (normal ventriculogram and end diastolic pressure < 10 mm Hg) and normal mitral valves by a double isotope scintigraphic method. Transferrin was labelled with indium^{-113m} and red cells with technetium^{-99m}, and scanning was performed over the lung fields and over the cardiac blood pool. A plasma protein accumulation index for transferrin in the lung fields was then calculated. In the control patients the mean index was 0·4 (0·3) $\times 10^{-3}$/min, and in the patients with severe chronic left heart failure it was significantly lower (− 0·1 (0·4) $\times 10^{-3}$/min; $p < 0·05$).

Thus pulmonary microvascular permeability as assessed by the plasma protein accumulation index is significantly reduced in severe chronic left heart failure. This may represent an adaptation protecting against pulmonary oedema when the pulmonary venous pressure is persistently raised.

Arteriographic underestimations of vessel diameter leading to overestimation of severity of stenosis

G L Pappageorgio, Norah Hudson, V J Redding, N B Jones
Department of Biomedical Engineering, University of Leicester, Groby Road Hospital, Leicester

Theoretical analysis of radiographic images in terms of signal to noise ratio shows a non-linear underestimation of the arterial image in arteriograms that is dependent on size. A study was undertaken to investigate whether arteriographic images of small vessels were distorted and if so to what degree. A series of radiographs was taken of small tubes of accurately known internal diameter (1–3 mm) filled with contrast medium. Comparison of the diameters of the tube images with the actual diameters showed an underestimation of the diameter, which was dependent on size: the smaller the tube the higher the underestimation of its diameter. Given that the underestimation of diameter becomes more severe in small vessels approaching the resolution limit of the imaging system, the error introduced in measuring the severity of stenosis, in which two vessels of unequal diameters are compared, may be quite considerable. An equation has been derived to compensate for the overestimation error. This may prove useful in assessing the severity of stenosis, and an automatic correction could be introduced in automated edge detecting systems.

Syndrome X: abnormal left ventricular filling during dipyridamole echocardiography

A Nadazdin, M Shahi, T Crake, R A Foale
Department of Cardiology, St Mary's Hospital, London

Alterations in left ventricular filling occur during myocardial ischaemia. To investigate whether these changes occur in patients with syndrome X we studied five normal subjects (group A), 20 patients with coronary artery disease (group B), and eight patients with syndrome X (group C). Left ventricular filling was assessed from early and atrial filling velocities by pulsed Doppler ultrasound. A high dose infusion of dipyridamole (0·9 mg/kg over 10 minutes) was used to provoke myocardial ischaemia. Blood pressure and 12 lead electrocardiograms were recorded every minute before, during, and after the infusion for 20 minutes. There were no differences in heart rate and blood pressure response between the three groups during the procedure. No patient showed electrocardiographic changes in group A; 11 of the 20 (55%) in group B and five of the eight (63%) in group C had ST segment depression. The mean maximum percentage decrease in early filling velocity was 3 (2·5), 9(10), and 14 (7) in groups A, B, and C respectively. Both groups B and C were significantly different from group A ($p < 0{\cdot}05$), but no difference existed between groups B and C. In groups A, B, and C no difference was found in the mean maximum percentage increase in atrial filling velocity (39 (26), 29 (26), 40 (16)) or mean maximum percentage decrease in the ratio of early filling velocity to atrial filling velocity (17 (8), 25 (5), 27 (7)).

Patients with syndrome X and coronary artery disease have a similar left ventricular filling response during infusion of dipyridamole. This may suggest that myocardial ischaemia occurs in patients with syndrome X.

Transoesophageal echocardiography: method of choice to visualise left atrial pathology

M A de Belder, G Leech, A J Camm
Department of Cardiological Sciences, St George's Hospital Medical School, London

Transoesophageal echocardiography (TOE) provides an ultrasound window directly adjacent to the left atrium and should be ideal for evaluating left atrial pathology. The first 203 TOE scans performed at this centre showed that 33 patients had abnormalities of either structure or flow in the left atrium (18 men, 15 women; mean age 64, range 35–83 years). TOE was performed in six patients because of a possible or definite atrial mass and in 22 patients to exclude a cardiac source of embolus. Ten patients were found to have echocardiographic patterns in the left atrial appendage or adjacent to the left atrial wall consistent with thrombus; 12 patients were found to have spontaneous contrast echoes in the left atrium, four of whom had echoes consistent with thrombus; in all but two of these patients transthoracic echocardiography (TTE) had not showed these findings. Seven patients were found to have a patent foramen ovale with contrast studies (only one was detected with colour flow mapping), three of which had been missed with TTE contrast studies. Four patients were found to have an excessively mobile atrial septum, one being frankly aneurysmal—this was apparent from the short axis TTE. In two of the cases of suspected atrial tumour the initial diagnosis was wrong: one patient was found to have an appreciable posterior mitral valve prolapse and the other was the patient with the atrial septal aneurysm. Two patients with a diagnosis of left atrial mass (on TTE one myxoma, one sarcoma) were further evaluated by TOE. Another patient who had a cerebrovascular accident after resection of a malignant lung tumour was found to have a posterior left atrial wall shadow consistent with a possible invading tumour or thrombus; this had not been detected by TTE.

We conclude that TOE is superior to TTE in the evaluation of left atrial pathology.

Outpatient transoesophageal echocardiography: technique, patient tolerance, and costs

G Leech, M A de Belder, A J Camm
Department of Cardiological Sciences, St George's Hospital Medical School, London

The main limitation of transthoracic echocardiography (TTE) is the poor quality of the image because of the inability of ultrasound to penetrate lung or bone. Transoesophageal echocardiography (TOE) uses a transducer at the end of a gastroscope. There are few clinical contraindications. To minimise the facilities needed and to maximise the numbers of patients who can be scanned in one session we have introduced outpatient TOE in unsedated patients. Patients are asked to starve for four hours before the study; topical hypopharyngeal anaesthesia is used and lignocaine gel smeared on to the transducer, which is inserted guided by the operator's fingers. Success is aided by careful explanation and good insertion technique. A complete cross sectional and colour Doppler study takes 5–10 minutes. No significant short or long term complications have occurred in 203 studies. A questionnaire was given to patients enquiring about their tolerance of the technique and their views about the use of sedation. Of the first 128 clinic patients, 82% found it "tolerable" or "mildly unpleasant" and 18% "unpleasant." Younger patients were more likely than older ones to find it unpleasant. Seven patients received sedation, three because they requested it, three because of initial intolerance, and one because of an elective prolonged scan; all were totally or partially amnesic of the scan. Of the others, 86% would have preferred no sedation for an outpatient study, although 26% would have preferred sedation for an inpatient study. Recent reports have shown the benefits of TOE in specific diseases, but the transducer is expensive. We estimate that we will perform 400–600 scans a year. With a predicted lifetime of five years, the use of the transducer carries a cost of £10–15 per scan; this will probably fall significantly in the future.

Is pulmonary artery banding obsolete for double inlet ventricle and tricuspid atresia?

R C G Franklin, I D Sullivan, R H Anderson, J E Deanfield
Hospital for Sick Children and Brompton Hospital, London

Subaortic stenosis in double inlet ventricle or tricuspid atresia almost always occurs with a dominant left ventricle, discordant ventriculoarterial connection, and unobstructed pulmonary blood flow. Pulmonary artery banding is said to be contraindicated in such patients as it may exacerbate or promote the development of subaortic stenosis. We studied 103 consecutive infants (56 with double inlet atresia, 47 with tricuspid atresia) with this anatomy (presenting 1972–87) to determine the effect of palliation on the development of subaortic stenosis. At presentation 27 of the 103 patients had subaortic stenosis ($>$ 10 mm Hg gradient at rest from left ventricle to aorta or ventricular septal defect $<$ 0·5 aortic valve diameter), either in isolation (11 patients) or with aortic arch obstruction (16 patients). Of the 76 patients without subaortic stenosis at presentation, 57 were palliated by either pulmonary artery banding with aortic arch repair (22 patients; median age 4 weeks) or isolated pulmonary artery banding (35 patients; median age 22 weeks). After pulmonary artery banding with aortic arch repair 17 of the 22 (77%) patients died by the age of 2 years and all of the five survivors developed new subaortic stenosis, which was evident in all of them by the age of 2 years. In contrast, after isolated pulmonary artery banding five of the 35 (14%) patients died aged under 2 years ($p < 0{\cdot}01$) and subaortic stenosis developed in only six out of 27 (22%) ($p < 0{\cdot}01$) survivors aged more than 2 years, being evident in all of them by 2 5 years (mean follow up 7·1 years). Of the remaining 21 patients, 17 of the 18 who have been reassessed to date fulfilled Fontan criteria.

Thus infants with double inlet atresia or tricuspid atresia and aortic arch obstruction have subaortic stenosis at presentation or inevitably develop it rapidly after conventional palliation. Vigorous initial operation, at higher risk, may be indicated. When subaortic stenosis and aortic arch obstruction are absent pulmonary artery banding provides effective palliation at reasonable risk to prepare most patients for definitive operation and should not be regarded as obsolete.

Value of transoesophageal echocardiography in adolescents and adults with congenital heart disease

G R Sutherland, R Geuskens, M A Taams,
E J Gussenhoven, J Hess, J Roelandt
Thoraxcenter, Erasmus University, Rotterdam,
The Netherlands

Precordial ultrasonography often yields inadequate results in older patients with complex congenital lesions because of a previous thoracotomy, chest deformity, or cardiac malposition. Transoesophageal echocardiography potentially circumvents these problems. Seventy four such patients (age range 10–56 years) with clinical problems and inadequate results from precordial studies underwent correlative outpatient transoesophageal echocardiography (imaging and colour flow). The lesions studied included intra-atrial baffles, atrial septal defects, Ebstein anomalies, Fontan procedures, atrioventricular defects, congenital mitral lesions, ventricular septal defects, subaortic obstruction, atrioventricular discordance, criss cross heart, and descending aortic lesions. Abnormalities of atrial appendange anatomy and systemic and pulmonary venous drainage were consistently defined, as were atrial septal defect morphology and an unsuspected range of atrial baffle abnormalities. Lesions of the atrioventricular junction were equally well defined, as was the chordal arrangement in criss cross hearts. Unique structural and flow information was also obtained after Fontan procedures and in complex subaortic obstruction. Problems arose because of the restricted imaging planes inherent in using transoesophageal echocardiography in the definition approach of ventricular septal defects, right ventricular outflow obstruction, descending aortic lesion, and extracardiac conduits. Image and flow masking due to prosthetic material was a problem in patients after operations.

We conclude that transoesophageal echocardiography is a major advance in the diagnosis and follow up of adolescent and adult patients with complex cardiac disease.

Is balloon dilatation the treatment of choice for aortic recoarctation?

I D Sullivan, S G Cooper, C Wren
Hospital for Sick Children, London, and
Freeman Hospital, Newcastle upon Tyne

From 1985 to 1988 balloon dilatation of aortic recoarctation was performed 47 times in 44 patients, a mean of 49 (SD 54) months after surgical repair. Initial surgery was performed in the neonatal period in 29 patients. The mean age at balloon dilatation was 4·9 (5·3) years (range 2 months–20 years), weight 18 (15) kg (range 2–72). The difference in systolic pressure across the recoarctation site decreased from 37 (15) to 14 (11) mm Hg ($p < 0·001$) immediately after balloon dilatation and was independent of the nature of the previous operation (subclavian flap ($n = 12$), resection with end to end anastomosis ($n = 21$), patch angioplasty ($n = 4$), multiple operation ($n = 5$)). Systolic pressure in the ascending aorta decreased from 120 (25) to 113 (20) mm Hg ($p = 0·02$). Pulse pressure in the descending aorta increased from 22 (7) to 36 (8) mm Hg ($p < 0·001$). Coarctation/aorta diameter increased from 0·45 (0·14) to 0·85 (0·16) ($p < 0·001$). At repeat catheterisation in 21 (49%) patients a mean of 12 (8) months after balloon dilatation there was a further reduction in the systolic pressure difference from 17 (11) to 12 (9) mm Hg ($p = 0·03$), with no further change in coarctation/aorta ratio. Aneurysm formation was evident in one patient immediately after balloon dilatation; this was unchanged at repeat study 15 months later. "New" aneurysms were apparent in 2/20 (10%) of the other patients restudied to date. Appearances in these three patients were unrelated to balloon size. There were no deaths related to the procedure. Three (7%) patients, all weighing less than 12 kg, had femoral artery occlusion.

Balloon dilatation provides good relief of obstruction with low morbidity. This compares favourably with the reported results of reoperation. Longer follow up is required to assess the importance of the aneurysms observed, but balloon dilatation remains our treatment of choice for recoarctation.

Morphology of double outlet right ventricle (DORV) shown by magnetic resonance imaging

J M Parsons, E J Ladusans, E J Baker,
Victoria Ayton, M A Smith, S A Qureshi,
R H Anderson, M J Tynan
Guy's Hospital, London

Nine patients with double outlet right ventricle (DORV) were studied with a 1·5 T magnetic resonance imaging system. Echocardiography was performed in all patients and angiography in five. Two patients underwent surgical correction and five palliation. Multiple thick (5 mm) sections gated to the patient's electrocardiograms were acquired in standard and oblique planes. The relation between great arteries; subarterial morphology; position and relation of the ventricular septal defects to the great arteries and attachments of the atrioventricular valves were assessed. The relative positions of the great arteries were identified in every case. The ventricular septal defect was identified as closely related to the pulmonary artery in four patients, to the aorta in three, and non-committed in one. In one patient with associated atrioventricular septal defect there was a large ventricular component. In one patient the ventricular septal defect had become restrictive and adherent tissue closing the defect could be seen. A single infundibulum was identified related to the pulmonary artery in three patients, one with subpulmonary stenosis, and to the aorta in two patients. A bilateral infundibulum was identified in two patients, with subaortic stenosis seen in one patient who had undergone banding of the pulmonary artery. A common atrioventicular valve was identified in the patient with atrioventricular septal defect. In the other patients separate atrioventricular valves were seen. In two patients the tricuspid valve apparatus could be seen attached to the crest of the venricular septum, but in no cases were straddling valves identified.

Magnetic resonance imaging correlated well with surgical and angiographic results and seemed to be particularly suited to showing the spatial relation between the ventricular septal defect and the great arteries and the relations between the great arteries.

Doppler analysis of blood flow in the superior vena cava: clinical and echocardiographic correlation

J M Parsons, E J Ladusans, S A Qureshi, Lok Y So, E J Baker, Lindsay Allan, M J Tynan
Guy's Hospital, London

Doppler velocities were recorded from the superior vena cava in 72 patients. Twenty six had normal hearts and 46 congenital heart disease, of whom 29 had undergone operation. Four patterns were recognised, which were correlated with clinical and echocardiographic findings. In four patients recordings were not suitable for analysis. Ten patients had a single systolic peak (first waveform). Forty six had a biphasic waveform with the systolic component greater than the diastolic component (second waveform). Eleven patients had a biphasic waveform but with the reversed pattern (third waveform). One patient had a triphasic waveform similar to that of the third pattern but with an additional presystolic component (fourth waveform). Findings associated with the first waveform included five normal hearts, one pericardial effusion, two small ventricular septal defects, one postoperative ventricular septal defect, and one postoperative ductus arteriosus. The third waveform was identified in eight patients who had undergone atrial redirection for complete transposition and had non-obstructed venous pathways and in one patient with atrioventricular septal defect, one with tetralogy of Fallot, and one with postoperative ventricular defect. The patient with the fourth (triphasic) waveform had undergone Mustard's operation and had pulmonary vascular disease. The remaining patients all had the second waveform. All patients with normal hearts had either the first or second waveform.

Doppler analysis is able to identify specific patterns of blood flow in the superior vena cava in differing clinical situations.

Complete heart block in children: How many will need a pacemaker?

Kim A Priestley, M J Tynan, P V L Curry
Guy's Hospital, London

Forty three children with complete heart block presented between 1972 and 1988. The complete heart block was probably congenital in 28 children (65%), occurred postoperatively in 14, and occurred after chickenpox myocarditis in one child. In contrast with the presentation of complete heart block in adults, the condition was discovered incidentally in 26 of the 43 children. The congenital complete heart block was discovered prenatally in eight children and was diagnosed at birth in a further four. It was, however, often discovered during infancy and childhood: in 10 patients because of a slow or irregular pulse, in four because of a heart murmur, and in two because of symptoms due to structural heart disease. Permanent pacemakers were eventually inserted in 27 children: all 14 children with postoperative complete heart block, 12 with congenital complete heart block, and the child with acquired complete heart block. The indications for insertion of a pacemaker in the 12 with congenital complete heart block were syncopal symptoms in seven (mean age 9 years, range 0·9–13·6), heart failure and failure to thrive in two (aged 0·8 years), and systemic emboli in one child aged 10·5 years. Two children without symptoms received a pacemaker, one during cardiac operation and the other as a prophylactic measure for subsequent orthopaedic operation. Of five children with congenital complete heart block and structural heart disease, three underwent implantation of a pacemaker and one cardiac transplantation.

Although often presenting as an incidental finding in children, complete heart block requires careful follow up as many children will need permanent pacing during childhood.

Efficacy of percutaneous balloon dilatation of the pulmonary outflow tract as palliation of tetralogy of Fallot

S A Qureshi, E J Ladusans, J M Parsons, E J Baker, M J Tynan
Department of Paediatric Cardiology, Guy's Hospital, London

We evaluated the efficacy of palliation in the tetralogy of Fallot by percutaneous balloon dilatation of the right ventricular outflow tract. Nine patients, mean age at balloon dilatation 9·4 months (range 0·6–16·4) and mean weight 6·9 kg (range 2·6–8·9), were treated. Palliation was required for hypercyanotic spells in five and for worsening cyanosis and polycythaemia in four. Successful dilatation was achieved in eight patients. The mean diameter of the pulmonary annulus measured angiographically was 9·3 mm (range 5–13) and the average ratio of balloon to annulus was 1·5 (range 1·2–1·8). Aortic oxygen saturation increased from 76 (SD 10·5) before to 88·4 (7·2) after dilatation ($p < 0\ 005$). Pulmonary artery saturation rose from 62 1 (13·3) to 79·4 (6·4) after balloon dilatation ($p < 0{\cdot}002$). The pressure gradient across the right ventricular outflow tract fell from 71·5 (12·2) to 56 3 (17·4) mm Hg immediately after dilatation ($p < 0{\cdot}07$). All patients had transient hypotension and arterial desaturation during inflation. In three patients transient ST elevation occurred during (two) or after (one) dilatation. No spells were encountered during or after dilatation. Attempts to cross the pulmonary valve in one patient resulted in infundibular perforation by the guide wire. There were no adverse sequelae from this and a Blalock-Taussig shunt was performed. Follow up after successful balloon dilatation ranged from 1·0 to 8·9 months (mean 4·6). Palliation was adequate in all of the patients, with three of them requiring a second procedure.

In conclusion, adequate palliation in tetralogy of Fallot is possible by balloon dilatation, thus avoiding a shunt operation. The long term effects on pulmonary artery growth require further evaluation.

Symmetrical aortoplasty repair for supravalvar aortic stenosis

G Angelini,* M Hazekamp, V Van Boven, H Huysmans, J Quaegebeur*
Thoraxcenter Academic Hospital, Rotterdam, Dijkzigt* and Thoraxcenter Academic Hospital, Leiden, The Netherlands

Surgical correction of supravalvar aortic stenosis is most commonly performed by patch enlargement of the right coronary or the non-coronary sinuses of Valsalva, or both. These procedures relieve the obstruction in most patients but do not restore the normal circular configuration of the aorta and hence the normal coaptation of the aortic valve leaflets. A different approach consisting of a symmetrical enlargement of the supravalvar stenotic ring was used in eight patients (five males; age range 3 to 46 years) whose preoperative left ventricle-aortic peak systolic gradient ranged from 130 to 40 mm Hg. After complete transection of the aorta just above the stenotic point the stenotic ring was divided in three places by incisions extending into each of the coronary sinuses of Valsalva. Individual U shaped pericardial patches were then used to produce widening of the three coronary sinus incisions. This resulted in a symmetrical enlargement of the aortic root and ascending aorta. The postoperative gradient ranged from 0 to 10 mm Hg. All of the patients survived the operation, seven remained symptom free, and one suffered aortic incompetence necessitating valve replacement. Excluding this patient, echocardiography at six months to 10 years postoperatively showed a residual gradient ranging from 10 to 25 mm Hg and normal aortic valve function.

Symmetrical aortoplasty repair achieves a lower postoperative gradient than previously described procedures. It more closely reconstructs the anatomical configuration of the aorta and thereby more completely restores the function of the aortic valve.

Expert answers to your questions in CARDIOLOGY

J. A. Cosh, J. V. Lever, Bath

Rheumatic Diseases and The Heart

1988. 112 figures. XIV, 250 pages. Hard cover DM 150,-. ISBN 3-540-19524-6

This is the first book to deal comprehensively with the involvement of the heart and great vessels in rheumatic diseases. The various rheumatic diseases are presented in successive chapters which cover the essential immunological and pathological basis for each disease, its extra-articular effects in general and the lesions of the heart and great vessels in particular. This book will bridge this gap in knowledge and prove of value to both rheumatologists and cardiologists.

Distribution rights for Japan: Iguku Shoin, Tokyo

O. M. Eliseev, Moscow

Cardiovascular Diseases and Pregnancy

Translated from the Russian by
E. Tarkhanova and G. Watts

1988. XII, 196 pages. Hard cover DM 124,-. ISBN 3-540-19174-7

The goal of this book is to provide obstetricians with necessary cardiological information and cardiologists with essential obstetric information to enable both specialists to make optimal decisions regarding the permissibility of pregnancy, management of pregnancy and labour, or termination of pregnancy, and selection of an adequate form of contraception in women with heart and vascular diseases.

Prices are subject to change without notice.

Springer-Verlag Berlin
Heidelberg New York London
Paris Tokyo Hong Kong

Heidelberger Platz 3, D-1000 Berlin 33 · 175 Fifth Ave., New York, NY 10010, USA · 8 Alexandra Rd, Wimbledon London SW19 7JZ, England · 26, rue des Carmes, F-75005 Paris · 37-3, Hongo 3-chome, Bunkyo-ku, Tokyo 113, Japan · Citicorp Centre, Room 1603, 18 Whitfield Road, Causeway Bay, Hong Kong

H. Manabe, Suita-shi; B. W. Zweifach, University of California; K. Messmer, University of Heidelberg (Eds.)

Microcirculation in Circulatory Disorders

1988. 283 figures. XIV, 551 pages. Hard cover DM 218,-. ISBN 3-540-70034-X

This book presents recent progress in microvascular disorders including cerebral, myocardial and peripheral tissue ischemia, multiple organ failure and gastroenterological disorders. Knowledge of microcirculation is essential in order to understand thoroughly the mechanism of organ disorders. This book successfully elucidates the pathophysiologic significance of microcirculation in ischemia and other diseases.

A. Radley, Loughborough

Prospects of Heart Surgery

Psychological Adjustment to Coronary Bypass Grafting

1988. 14 figures. XII, 246 pages. (Contributions to Psychology and Medicine). Hard cover DM 98,-. ISBN 3-540-96721-4

This volume reports on a study of how patients and their spouses adjusted to the prospect, and then to the outcome, of coronary graft surgery. The book offers, as one of its main contributions, a social-psychological approach to the study of illness in general. It sets out a new methodology which might be applied in a number of illness contexts.

G. Schettler, R. B. Jennings, E. Rapaport, N. K. Wenger, R. Bernhardt (Eds.)

Reperfusion and Revascularization in Acute Myocardial Infarction

Veröffentlichungen aus der Geomedizinischen Forschungsstelle der Heidelberger Akademie der Wissenschaften

1988. 66 figures, 43 tables. XIX, 272 pages. (Sitzungsberichte der Heidelberger Akademie der Wissenschaften, Jahrgang 1988, Supplement 2). Hard cover DM 134,-. ISBN 3-540-50022-7

Contents: Pathophysiology of Salvage of Ischemic Myocardium by Reperfusion. - Thrombolysis in Acute Myocardial Infarction. - Percutaneous Transluminal Coronary Angioplasty. - Coronary Bypass Surgery. - Rehabilitative Care After Myocardial Revascularization.

D. A. Redel, University of Bonn

Color Blood Flow Imaging of the Heart

1988. 214 figures. VII, 130 pages.
Hard cover DM 298,-.
ISBN 3-540-16521-5

This book looks at the newly developed technique of color blood flow imaging (CBFI) - a noninvasive ultrasonic method which will change essentially the diagnostic procedures in cardiology in the years to come. The reader is introduced to this fascinating method by typical findings of CBFI in all common types of heart disease to an extent not available in any other publication.

Distribution rights for Japan: Igaku Shoin, Tokyo

H.-P. Schultheiss, Munich (Ed.)

New Concepts in Viral Heart Disease

Virology, Immunology and Clinical Management

1988. 190 figures, 58 tables. XI, 504 pages.
Hard cover DM 248,-.
ISBN 3-540-19179-8

Recent progress in research on virus tropism and (virus) persistance is reported. The main topics of the book concern post-infectious autoimmunity and genetic and patho-physiological aspects. The problem of obtaining a diagnosis in this multifaceted disease is discussed and therapeutic approaches are critically reviewed.

tm 5129/SF

K. O. Stumpe, K. Kraft, A. I. Faden, University of Bonn (Eds.)

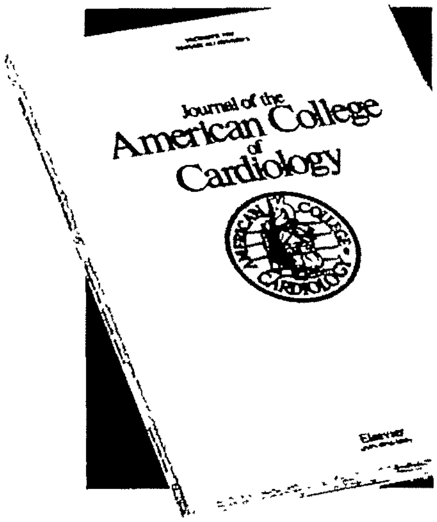
Opioid Peptides and Blood Pressure Control

1988. 90 figures. VIII, 300 pages.
Soft cover DM 149,-.
ISBN 3-540-18935-1

This book provides current knowledge on the influence of endogenous opioid peptides on blood pressure regulation. In view of the rapid increase in knowledge in the field, it is important that scientists in blood pressure research as well as specialist clinicians have access to such a comprehensive survey.

Springer

A Standard of Excellence


Journal of the American College of Cardiology

Journal of the American College of Cardiology

Editor-in-Chief: Simon Dack, M.D.

Recognized worldwide as a major voice in cardiology, **JACC** should be #1 on your must-read list.

JACC's quality is assured.
As the official journal of the American College of Cardiology, **JACC** must meet ACC standards of excellence. Because of its outstanding editorial leadership and rigorous selection standards, **JACC** is trusted by its over 20,000 readers monthly.

JACC covers a broad spectrum.
Reporting on advances in adult and pediatric cardiology, diagnostic procedures, drug therapy, cardiovascular surgery and basic research, every issue of **JACC** gives readers a comprehensive look at cardiovascular medicine. **JACC** also presents high-quality symposia on special topics

JACC is clinically oriented.
Every article in **JACC** stresses the clinical significance of important new information on cardiovascular disease. In addition, reviews, editorials and commentary put it all in perspective.

Find out for yourself why the **Journal of the American College of Cardiology** is the #1 journal in cardiology. Use the coupon below to enter your subscription today!

ORDER FORM

1989 Subscription Information
Journal of the American College of Cardiology
Volumes 13 and 14 (14 issues plus one supplement) 1989
ISSN 0735-1097

Please enter my subscription at the following rate:
☐ Personal rate $77 00* ☐ Institutional rate $114 00
☐ In-training rate $49 00

For air delivery in the U S , Canada, or Mexico, add $90 00 Subscribers outside the U S should add $45 00 for surface delivery, $100 00 for surface airlift delivery to Europe, $130 00 for surface airlift to Japan, or $265 00 for air delivery to the rest of the world

JACC is abstracted/indexed by *Index Medicus, Current Contents/Life Sciences, Current Contents/Clinical Practice, Excerpta Medica, Biological Abstracts, Chemical Abstracts, and Science Citation Index.*

PAYMENT
Enclosed is my: ☐ personal check ☐ bank draft

Please charge to:
☐ American Express ☐ MasterCard (issuing bank #______)
☐ VISA Account # ______ Expires ______
Signature ____________

☐ **Please bill me.** (Orders from non-U S customers must be prepaid)

Name ____________
Address ____________

City ____________
State ____________
Country/Zip/Postal Code ____________

For sample copies, send to:

In North America:
Elsevier Science Publishing Co , Inc , P O Box 882,
Madison Square Station, New York, NY 10159

In the rest of the world:
Elsevier Science Publishers, Direct Mail Department,
P O Box 211, 1000 AE Amsterdam, The Netherlands

Send subscription orders to either your usual supplier or to the New York address.

Note Subscription rates valid until December 31, 1989 Please allow 6-8 weeks for delivery of the first issue

*The personal rate is available to individuals at home addresses or medical institutions, and must be prepaid

10/88 V9AL BILL830A

Elsevier

Br Heart J 1989;**61**:483

Correspondence

Influence of age on Doppler echocardiographic indices of left ventricular diastolic function

Sir,

We read with interest Spirito and Maron's article (1988;59:672–9). Their conclusions about the effect of aging on diastolic left ventricular filling accord with ours.[1] We showed that atrial filling fractions increased significantly with age in normal subjects from 12% to 46%, and we concluded that "age-corrected nomograms are mandatory in assessing atrial filling fraction in individual patients". We also found, as did others,[2] that mitral regurgitation can augment early diastolic filling and alter the left ventricular filling pattern. Even slight mitral regurgitation can influence the inflow pattern and can lead to apparent normalisation of early diastolic filling in patients with disturbed diastolic function. This implies that when Doppler echocardiography is used to study left ventricular filling, mitral regurgitation should be taken into account, especially as it can be clinically silent.

Edward G Abinader,
Dawod S Sharif,
Heart Institute and Coronary Care Unit,
Haifa Medical Centre,
Faculty of Medicine,
Technion, Haifa, Israel.

References

1 Kuo LC, Quinones MA, Rokey R, Sartori M, Abinader EG, Zoghbi WA. Quantification of atrial contribution to left ventricular filling by pulsed Doppler echocardiography and the effect of age in normal and diseased hearts. *Am J Cardiol* 1987;59:1174–8.
2 Shaikh AM, Lavine SJ. Effect of mitral regurgitation on diastolic filling with left ventricular hypertrophy. *Am J Cardiol* 1988;61:590–4.

Br Heart J 1989;**61**:484

Notices

British Cardiac Society

The Annual General Meeting will take place in Torquay on 22 to 25 May 1990.

Cardiac ultrasound

The 4th Bristol Cardiac Ultrasound Course will be held at Bristol General Hospital. There are two modules which can be attended individually if desired: on 12 and 13 July 1989 on Cardiac imaging (M mode and cross sectional) and on 14 and 15 July 1989 on Doppler echocardiography (including colour flow). Further details from Dr Peter Wilde, Consultant Radiologist, Department of Radiodiagnosis, Bristol Royal Infirmary, Bristol BS2 8HW. Telephone (0272) 230000 Ext 2130.

Pakistan Cardiac Society

The 9th biennial International Congress of Cardiology organised by the Pakistan Cardiac Society will take place in Lahore on 7 to 10 December 1989. For information write to the organising secretary of the Congress at the Department of Cardiology, Mayo Hospital, Lahore, Pakistan.

Correction

Cardiac surgery for patients aged 65 years and older: a long term survival analysis *S Livesey, N Caine, D J Spiegelhalter, T A H English, J Wallwork*—The authors apologise for omitting in their paper published in the December 1988 issue (volume 60: pages 480–4) thanks to Mr B B Milstein for his help and acknowledgement to the cardiologists at Papworth Hospital who selected and referred the patients for operation.

June 1989 Vol 61 No 6

British Heart Journal

A monthly journal of cardiology published in association with the British Cardiac Society

Outcome in patients with recurrent restenosis after percutaneous transluminal balloon angioplasty *J J Glazier, T R Varricchione, T J Ryan, N A Ruocco, A K Jacobs, D P Faxon* **485**

Electrocardiographic evidence of myocardial salvage after thrombolysis in acute myocardial infarction *K J Hogg, K R Lees, R S Hornung, C A Howie, F G Dunn, W S Hillis* **489**

Silent myocardial ischaemia in patients referred for coronary bypass surgery because of angina: a comparison with patients whose symptoms were well controlled on medical treatment *D Mulcahy, J Keegan, D Lindsay, J Sparrow, A Park, C Wright, K Fox* **496**

Initial experience with a microprocessor controlled current based defibrillator *G W N Dalzell, S R Cunningham, J Anderson, A A J Adgey* **502**

Central haemodynamic changes after a meal *H Kelbæk, O Munck, N J Christensen, J Godtfredsen* **506**

The QT interval in atrial fibrillation *G R Pai, J M Rawles* **510**

Right ventricular infarction: diagnostic accuracy of electrocardiographic right chest leads V3R to V7R investigated prospectively in 43 consecutive fatal cases from a coronary care unit *H R Andersen, E Falk, D Nielsen* **514**

Cold intolerance in patients with angina pectoris: effect of nifedipine and propranolol *I Peart, R E Bullock, C Albers, R J C Hall* **521**

Clinical, haemodynamic, and pharmacological effects of withdrawal and reintroduction of digoxin in patients with heart failure in sinus rhythm after long term treatment *S E Pugh, N J White, J K Aronson, D G Grahame-Smith, J G Bloomfield* **529**

Anomalous subaortic position of the brachiocephalic (innominate) vein: a review of published reports and report of three new cases *L M Gerlis, S Y Ho* **540**

Case reports

- Injury to a saphenous vein graft during removal of a temporary epicardial pacing wire electrode *C Price, D J M Keenan* **546**
- Severe haemolysis after percutaneous closure of a ductus arteriosus (arterial duct) *E J Ladusans, I Murdoch, J Franciosi* **548**
- Percutaneous transluminal balloon dilatation of the mitral valve in pregnancy *R Smith, D Brender, M McCredie* **551**

Notices **553**

Correspondence **554**

List of advisers **555**

Index **557**

British Medical Association

ASTM CODEN: BHJUAV 61(6) 485–583 (1989)
ISSN 0007-0769

British Heart Journal

EDITOR Dennis Krikler ASSISTANT EDITORS M J Davies, Kim Fox, Peter Mills

EDITORIAL COMMITTEE
Clive P Aber Kate Bull Keith Dawkins Alan B Houston Barry R Keeton Michael Marmot
Alexander L Muir Paul J Oldershaw Philip A Poole-Wilson David B Shaw
Tom Treasure David E Ward John Watkins Peter Wilde
Editor: *British Medical Journal* Editor: *Cardiovascular Research*

TECHNICAL EDITOR Jane Dawson EDITORIAL ASSISTANT Anne Oliver
STATISTICAL ADVISER Stephen J W Evans

Notice to contributors

Papers relating to the heart and circulation should be sent in triplicate to the Editor, British Heart Journal, BMA House, Tavistock Square, London WC1H 9JR, and be prepared according to the *Uniform requirements for manuscripts submitted to biomedical journals* (Vancouver agreement) (*Br Med J* 1988;**296**:401–5). Authors are asked to complete a copy of the checklist provided (1988;**59**:47 (January issue)) when submitting their manuscripts for publication. The reference number given on the acknowledgement postcard sent out by the editorial office should be quoted on all subsequent correspondence and telephone inquiries. A covering letter must be signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. All authors will be required to transfer copyright of their articles to the journal before publication. (All material for possible publication (including Letters to the Editor) *must* be typed in *double spacing* with 4 cm margins.)

Ethical standards

Authors are expected to comply with the code of ethics known as the Declaration of Helsinki. Where appropriate, manuscripts should include a statement that the research protocol has been approved by the locally appointed ethics committee and that the informed consent of the subjects has been obtained.

Case reports should convey only the essential facts of a case and the discussion and bibliography be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and include no more than two Figures.

Abbreviations should *not* be used in the text, except for mathematical calculations and units of measurement.

References must be cited precisely according to the Vancouver agreement and be typed in *double spacing*. As a general rule, no more than three references should be cited for any one statement.

Authors are responsible for the accuracy of any references cited: these should be checked at source or with the listing in Index Medicus.

Units of measurement

All haematological and clinical chemistry measurements should be given as SI units. Blood pressures should be given in mm Hg. Measurements of length, height, weight, and volume should be reported in metric units and temperatures should be reported in degrees Celsius.

Tables must be typed on separate sheets and not in the text. Titles should be provided, and all abbreviations used must be given in full in a footnote.

Illustrations (for general requirements, please refer to *Br Heart J* 1984; **51:** 1–6).

Electrocardiograms: Black and white prints only should be sent and not the original tracings. If several tracings are grouped in a single Figure only a few complexes should be shown; the width should not exceed 14 cm unless a reduction in scale is possible.

Echocardiograms: Since these will be reproduced at a width of 7 cm or less all unnecessary or irrelevant detail (such as electronic writing) should be removed. Labelling must be superimposed directly on to the print itself and only where essential be shown on an accessory drawing. Echocardiograms obtained with 30° sector scans or bistable equipment or recorded on ultraviolet paper are not suitable for publication.

Figure legends must include an explanation of all abbreviations used in the Figure.

Copyright permission to reproduce material published elsewhere must be obtained in writing and acknowledged in the manuscript.

Proofs of articles accepted for publication will be sent for the author's approval. Proof corrections should be kept to a minimum.

Notice to subscribers

British Heart Journal is published monthly. The annual subscription rates are £97.00 inland and £113.00 overseas (USA $182·00). Combined rate: *British Heart Journal* and *Cardiovascular Research* £184 inland and £214 overseas (USA $350·00). Orders should be sent to The Subscription Manager, *British Heart Journal*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card. (For the convenience of readers in the USA subscription orders ($182) with or without payment may also be sent to British Medical Journal, Box 560B, Kennebunkport, Maine 04046. All inquiries, however, must be addressed to the Publisher in London.) **All copies are despatched by air-speed.** First class rates available on request.

COPYRIGHT © 1989 by the *British Heart Journal*. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without the prior permission of the *British Heart Journal*.

Second class postage paid, Rahway NJ Postmaster: send address changes to: British Heart Journal c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

Br Heart J 1989;61:485-8

Outcome in patients with recurrent restenosis after percutaneous transluminal balloon angioplasty

JAMES J GLAZIER, THOMAS R VARRICCHIONE, THOMAS J RYAN,
NICHOLAS A RUOCCO, ALICE K JACOBS, DAVID P FAXON

From the Evans Memorial Department of Clinical Research and the Department of Medicine, Boston University Medical Centre, Boston, Massachusetts, USA

SUMMARY The records of 1162 consecutive patients undergoing their first percutaneous transluminal coronary angioplasty at a centre between March 1980 and June 1987 were reviewed. Initial angioplasty was successful in 1011 patients (87%). In 202 (20%) symptomatic restenosis developed. Of these, 196 were treated with redilatation; this was successful in 181 (92%). After a second dilatation, restenosis developed in 47 patients (26%). Of these, 41 (87%) were treated with a third angioplasty, with primary success in 38 (93%). A further restenosis developed in 13 of these 38 patients (34%). Eight patients were treated with a fourth angioplasty with restenosis in four (50%). Two of these four patients underwent a fifth angioplasty (with continuing success at long term follow up in both). Overall, 14 of the 47 (30%) patients who developed restenosis twice were eventually treated with coronary bypass surgery. Most patients (33), however, were treated only with repeated angioplasties. Of these 33 patients, 27 were treated with a third angioplasty, four with a fourth procedure, and two with a fifth. Twenty-nine (88%) were symptom free at a mean follow up of 28 (range 8 to 86) months. The combined success rate for a third, fourth, and fifth angioplasty was 94%.

These data suggest that most patients with recurrent restenosis after angioplasty may be managed successfully and safely with repeated redilatations.

Since the introduction of coronary balloon angioplasty a decade ago[1-3] the indications for the procedure have widened considerably, the success rate has increased, and the complication rate has fallen.[4] Despite these impressive advances, restenosis remains the major drawback of the technique, occurring in approximately 30% of patients who have a successful initial angioplasty.[5 6] Treatment of restenosis with a repeat angioplasty is highly successful (greater than 95%[7]). Furthermore, it seems that a second recurrence is no more likely than a first.[7-9] Accordingly, most physicians recommend a repeat angioplasty for restenosis.[8] Less, however, is known about the treatment of patients who have a further restenosis after a second angioplasty. With the high annual growth in coronary angioplasty procedures patients with restenosis after a second angioplasty will become more common. We report our experience in the management of 47 patients with clinical restenosis after a second angioplasty and the long term outcome in these patients.

Patients and methods

Between March 1980 and June 1987 a total of 1162 patients underwent coronary angioplasty at our centre. Initial angioplasty was successful in 1011 patients. Clinical restenosis developed in 202 (20%). At our centre, after angioplasty, patients are followed closely by functional testing for the development of symptoms or signs of myocardial ischaemia. If evidence of ischaemia develops, cardiac catheterisation is performed to verify the occurrence of restenosis.

We defined restenosis as the recurrence of angina with angiographic documentation of >50% stenosis at a site with primary success. One hundred and ninety six of the 202 patients with clinical restenosis were treated with a second angioplasty procedure.

Requests for reprints to Dr David P Faxon, Section of Cardiology, The University Hospital, Boston, Massachusetts 02118, USA.

Accepted for publication 6 February 1989

The decision to proceed with a repeat angioplasty was determined entirely by the patient and referring physician. Successful angioplasty (defined as a reduction in diameter stenosis to <50% in the absence of myocardial infarction, death, or bypass surgery during hospital stay) was achieved in 181 (92%). There was a further recurrence in 47 (26%) of these 181 patients. We studied these 47 patients with recurrent restenosis of a lesion initially treated by angioplasty. Tables 1 and 2 show the clinical and angiographic features in these patients.

FOLLOW UP

After angioplasty patients attend our centre as outpatients every six months for a physical examination and symptom limited treadmill exercise test. Because the unit is a referral centre for more than twenty community hospitals, a large proportion (38%) of our patients with recurrent restenosis had been followed up at another hospital after their last angioplasty. We established contact with these patients by a postal questionnaire and/or telephone contact in April 1988.

Results

OBSTRUCTIVE LESIONS

Sixty four lesions in 47 patients were successfully dilated at initial angioplasty (table 2) and 55 of these were redilated. Fifty lesions restenosed both after first and second angioplasty. Of these lesions undergoing recurrent restenosis, 26 (52%) were located in the left anterior descending artery (10 in the proximal segment), 13 (26%) in the right coronary, 10 (20%) in the circumflex, and one in a graft vessel.

MANAGEMENT OF SECOND RESTENOSIS

Of the 47 patients with a second restenosis of their initially angioplastied lesion(s), six chose to be treated with coronary graft bypass surgery and 41 had a third angioplasty. Angioplasty was successful in 38 of these 41 patients (93%). Of the three patients in whom a third angioplasty was unsuccessful, two developed abrupt reocclusion requiring emergency coronary bypass graft surgery and one had a fatal cardiac arrest 24 hours after the procedure (table 3). Restenosis occurred in 13 (34%) of the 38 patients who had a successful third angioplasty.

Table 1 *Baseline clinical data in the study patients with recurrent restenosis*

Variable	*Data*
Patients (no)	47
Mean (SD) age (yr) (range)	54 (10) (39–78)
Men	41 (87)
Hypertension (>140/>95 mm Hg)	23 (49)
Cigarette smoking:	
Current	8 (17)
Former	15 (32)
Family history CAD	23 (49)
Hypercholesterolaemia	16 (34)
Previous myocardial infarction	24 (51)
Angina status (Canadian Heart Association classification)	
Unstable	16 (34)
Stable class III–IV	25 (53)
Stable class I–II	6 (13)

Numbers in parentheses are percentages. CAD, coronary artery disease.

Table 2 *Baseline angiographic data in the study patients*

Finding	*No (%)*
One vessel disease	26 (55%)
Two vessel disease	15 (32%)
Three vessel disease	6 (13%)
Left ventricular ejection fraction (%) (SD and range)	64 (14) (20–84)
Location of lesions (n = 64) dilated (according to vessel):	
Left anterior descending	30 (proximal = 10)
Circumflex	18
Right coronary	15
Graft	1
Single lesion dilatation	35 (74%)
Multilesion dilatation	12 (26%)

TREATMENT OF A THIRD RESTENOSIS

Eight of the 13 patients with a third restenosis were treated with a fourth angioplasty, four with bypass surgery, and one with medical management. Initial success was obtained in all patients with a fourth angioplasty, but restenosis developed in four (50%) (table 3).

TREATMENT OF A FOURTH RESTENOSIS

Two patients were treated with a fifth angioplasty (successful in both) and two with a bypass operation.

SUMMARY OF RESULTS

Of the 47 patients who developed restenosis twice, 14 (30%) were eventually treated with coronary graft bypass surgery (12 electively and two as emergencies). Most (33), however were treated only with

Table 3 *Outcome of patients with restenosis*

RS	*Rate (%)*	*No*	*1° CABG*	*PTCA*	*Em CABG*	*Prim succ*	*Sus succ*
1st	20	202	6	196	6 (3%)	181 (92%)	134
2nd	26	47	6	41*	2 (4%)	38 (93%)	23
3rd	34	13	4	8	0	8 (100%)	4 (1)‡
4th	50	4	2	2	0	2 (100%)	2

*One patient died.
‡One patient treated medically.
RS, restenosis; 1°CABG, initial treatment with coronary bypass surgery; PTCA, initial treatment with percutaneous transluminal coronary angioplasty; Em CABG, emergency coronary bypass surgery; Prim succ, primary success, Sus succ, sustained success after PTCA.

repeated angioplasty. Of these 33 patients, 27 had three angioplasty procedures, four had four procedures, and two had five procedures.

FOLLOW UP

Of the 33 patients treated only with repeated angioplasty (table 3), 29 (88%) remain well and angina free at a mean follow up period of 28 (range 8–86) months. In three patients (each treated with three angioplasty procedures) angina has recurred. One of these patients had a myocardial infarction and documentation of a third restenosis of his graft lesion. However, further revascularisation was not attempted in this patient, who has moderate symptoms on medical treatment. The other two patients have mild symptoms which are adequately controlled on medical treatment. In addition, two patients reported occasional atypical chest pain after their last angioplasty. There was no evidence of restenosis, however, in either patient at repeat angiography. Both patients treated with a fifth angioplasty remain well and symptom free with no evidence of inducible ischaemia, as assessed by repeated exercise testing, 15 and 32 months after the last procedure. There have been no late deaths and only the patient mentioned earlier has had a myocardial infarction since the last angioplasty.

Of the 14 patients who were eventually treated with bypass surgery, three (21%) have had a recurrence of their symptoms. One of these three patients had a myocardial infarction 10 months after operation. There were no deaths in this patient group at a mean follow up of 27 (range 8–48) months.

Discussion

Our observations suggest that most patients with recurrent restenosis can be managed safely and effectively with repeated angioplasty. Of the 47 patients with a second restenosis, 33 (70%) were treated only with angioplasty and 29 (88%) were well and symptom free at long term follow up. Furthermore, the primary success rate for a third angioplasty was very acceptable (93%), as was the combined success rate (94%) for third, fourth, and fifth angioplasties.

Jolly *et al* reported a similar recurrent restenosis rate (4·3% in their series[10] and 4% in ours). We elected to perform a third angioplasty in most (87%) of our patients with a second restenosis, whereas Jolly *et al* treated most (58%) of such patients with coronary bypass surgery. Jolly *et al* reported that their choice of treatment for patients with a second restenosis seemed to be influenced more by the opinion of the cardiologist and the wishes of the patient than by clinical or angiographic factors, as was the case in our study. As repeat angioplasty becomes more accepted, it is likely that an increased proportion of such patients will choose repeat angioplasty rather than bypass surgery.

Our success rate (93%) and restenosis rate (34%) after third angioplasty accord with those of other centres. Terstein *et al* reported on 74 patients undergoing a third angioplasty.[11] Primary success was achieved in 69 (93%) patients and there was restenosis in 28 (41%). Jolly *et al* reported primary success in 33 (92%) of 36 patients and recurrence in 11 (33%).[10] Abi-Mansour *et al* documented restenosis in four (24%) of 17 patients after a successful third angioplasty.[12] Accordingly, it seems that the primary success rate, complication rate, and restenosis rate after a third angioplasty are similar to those after first or second angioplasty.

A further angioplasty was deemed to be technically feasible in all 12 patients in our study who eventually had elective coronary bypass surgery. Indeed, in all, the decision to proceed to bypass surgery rather than attempt a further angioplasty seemed to be determined more on the basis of patient and/or physician preference rather than angiographic factors.

We applied a hypothetical management model to our study to see what the outcome of treating these patients with repeated angioplasty would be. This model limited the maximum number of angioplasties performed in any one patient to five and assumed restenosis rates of approximately 20%, 30%, 35%, 50%, 50% for successive angioplasties. The general success rate for a second or subsequent angioplasty was assumed to be approximately 94%. Application of this schema to a hypothetical population of 1000 patients with a successful initial angioplasty (figure) forecasts that at some time primary success at angioplasty will not be obtained in 17 patients and that four patients will need five procedures to achieve long lasting revascularisation. Overall, coronary angioplasty will eventually fail in 21 (2·1%) of the hypothetical cohort of 1000 patients.

Whatever the projected outcome not all patients will be prepared to undergo repeated redilatations, and some will elect for revascularisation with coronary graft bypass surgery. Similarly, the development, within individual patients, of progressively more severe lesions with each subsequent redilatation may make further attempts at redilatation more difficult and they will eventually need bypass operations. In addition, the occurrence of progressively more complex as well as more severe lesions with successive redilatations may increase the restenosis rate because of greater vessel damage. This latter consideration may, in part, account for the increasing restenosis rate seen, with each subsequent redilatation, in our study patients.

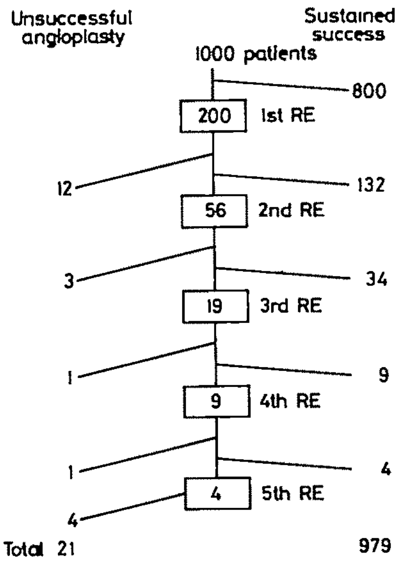


Fig 1 *Hypothetical model for the management of restenosis with angioplasty only. This was applied to a hypothetical cohort of 1000 patients with successful initial angioplasty. The assumptions on which this model is based are detailed in the text. RE, restenosis.*

Although our experience suggests that recurrent restenosis may be managed successfully with repeated redilatations, the cost effectiveness of such a management strategy must also be considered. Several studies have compared the cost effectiveness of initial revascularisation with coronary angioplasty and with that of coronary graft bypass surgery.[13 14] The results of these studies indicate that over a follow up period of 12 months angioplasty is the more cost effective method.[13 14] We do not know, however, whether the additional costs and long term outcome of patients undergoing two or more redilatations for recurrent restenosis are equivalent to those in patients who have bypass surgery after developing a second restenosis. These issues will have to be fully investigated before definitive guidelines on the management of recurrent restenosis can be drawn up.

Coronary balloon angioplasty is increasingly used as an alternative to coronary bypass graft surgery in the treatment of selected patients with coronary occlusive disease.[4] Indeed, in the United States, the number of coronary angioplasty procedures performed increased from 39 000 in 1983 to nearly 150 000 in 1987 (report from the Committee for Professional and Hospital Activities, Ann Arbor, Michigan). Despite the low incidence of recurrent restenosis the volume of coronary angioplasty procedures will increase the number of patients with repeat restenosis in the next few years. To date, there have been few guidelines on the management of patients with recurrent restenosis. Our experience suggests that patients are generally best treated by repeat angioplasty. Although some of our patients with recurrent restenosis were eventually treated with coronary bypass surgery, most remained symptom free at long term follow up after a third, fourth, or even fifth angioplasty.

References

1 Gruentzig AR, Myler RK, Hanna EH, Turina MI. Coronary transluminal angioplasty [Abstract]. *Circulation* 1977;55–56(suppl III):III–84.
2 Gruentzig AR. Transluminal dilatation of coronary artery stenosis. *Lancet* 1978;i:263.
3 Gruentzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med* 1979;301:61–8.
4 Myler RK, Shaw RE, Stertzer SH, Clark DA, Fishman J, Murphy MC. Recurrence after coronary angioplasty. *Cathet Cardiovasc Diagn* 1987;13:77–86.
5 Holmes DR, Vliestra RE, Smith HC, *et al.* Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA registry of the National Heart, Lung and Blood Institute. *Am J Cardiol* 1984;53:77C–81C.
6 Leimgruber PP, Roubin GS, Hollman J, *et al.* Restenosis after successful coronary angioplasty in patients with single vessel disease. *Circulation* 1986;73:710–8.
7 Meier B, King SB III, Gruentzig AR, *et al.* Repeat coronary angioplasty. *J Am Coll Cardiol* 1984;4:463–6.
8 Williams DO, Gruentzig AR, Kent KM, Detre KM, Kelsey SF, To T. Efficacy of repeat percutaneous transluminal coronary angioplasty for coronary restenosis. *Am J Cardiol* 1984;53:32C–5C.
9 Black AJR, Anderson HV, Roubin GS, Powelson SW, Douglas JS, King SB III. Repeat coronary angioplasty: correlates of a second restenosis. *J Am Coll Cardiol* 1988;4:714–8.
10 Jolly P, Bonan R, Palisaitis D, *et al.* Treatment of recurrent restenosis with repeat transluminal coronary angioplasty. *Am J Cardiol* 1988;61:906–9.
11 Terstein PS, Hoover C, Lignon B, *et al.* Repeat restenosis: efficacy of the third and fourth coronary angioplasty [Abstract]. *J Am Coll Cardiol* 1987;9:63A.
12 Abi-Mansour P, Whitworth HB, Hoffmeister J, Douglas JS, King SB. Initial and late outcome after a third coronary angioplasty (PTCA) for recurrent native coronary artery stenosis [Abstract]. *Circulation* 1985;72(suppl II):III–141.
13 Kelly ME, Taylor GJ, Moses HW, *et al.* Comparative cost of myocardial revascularisation: percutaneous transluminal angioplasty and coronary artery bypass surgery. *J Am Coll Cardiol* 1985;5:16–20.
14 Reeder GS, Krishan I, Nobrega FT, *et al.* Is percutaneous coronary angioplasty less expensive than bypass surgery? *N Engl J Med* 1984;311:1157–62.

Br Heart J 1989;**61**:489–95

Electrocardiographic evidence of myocardial salvage after thrombolysis in acute myocardial infarction

K J HOGG, K R LEES, R S HORNUNG, C A HOWIE, F G DUNN, W S HILLIS

From the Department of Materia Medica, University of Glasgow, Stobhill General Hospital, Glasgow

SUMMARY There is a need for a simple clinical measurement that will indicate the extent of myocardial salvage after successful thrombolysis. This study examined whether coronary artery reperfusion reduced the infarct size as assessed electrocardiographically after thrombolytic treatment. The sum of the (∑) ST segment area in leads showing ST segment elevation in the 12 lead electrocardiogram at presentation was used as an index of potential myocardial injury (initial ischaemic index). The evolved infarct size at 48 h was assessed by a QRS scoring system. Two groups of patients, both admitted with anterior myocardial infarction within 6 h of onset, were studied. Group 1 (n = 35) received analgesia only and group 2 (n = 33) received thrombolytic treatment either by the intracoronary (streptokinase, n = 13) or intravenous route (anistreplase, n = 20). Reperfusion was assessed angiographically. The mean (SD) potential infarct size assessed by the initial ischaemic index was similar in both groups (group 1, ∑ ST area = 115 (60) mm^2 and group 2 = 126 (77 mm^2). The QRS score representing evolved infarct size was significantly lower in the treated group (4·1 (2·5)) than in group 1 (7·8 (2·6)). The 95% confidence intervals for QRS scores based on the admission ∑ ST area from patients with successful reperfusion were applied to a third set of patients (n = 22) to test the ability of the admission ST area (myocardial injury) to predict the QRS score accurately . While patients with successful reperfusion had significantly lower QRS scores than those who did not (4·5 (3·1) *v* 9·3 (3·4)), the wide confidence intervals caused by inter-individual variability precluded an accurate prediction of the QRS score in an individual from the ∑ ST area at time of presentation. There was no difference in infarct size in patients treated early (⩽3 h) (QRS score 4·2 (2·8)) or later (3–6 h) (4·1 (2·1)).

This study provides evidence that sequential electrocardiographic changes are reduced in patients with anterior myocardial infarction who achieve reperfusion after thrombolytic treatment and that this benefit is shown with treatment given up to six hours after infarct onset. None the less, the relation between the initial ischaemic index and the evolved QRS score has wide confidence intervals, reflecting inter-individual variability, and does not allow the prediction of a QRS score in an individual patient.

Thrombolytic treatment is being widely used in patients with acute myocardial infarction; the aims of treatment are coronary artery reperfusion[1 2] and maintenance of left ventricular function.[3] Brief, high dose intravenous infusion of streptokinase is a feasible treatment that may be given in all coronary care units and has reduced mortality in hospital.[4 5]

Non-invasive methods to confirm both coronary artery reperfusion and the degree of myocardial salvage would be helpful in planning long term management. We have already reported on the use of 12 lead electrocardiograms to determine reperfusion.[6] ST segment elevation is an electrocardiographic marker of coronary artery occlusion, and the natural course of the development of sequential electrocardiographic changes after clinical infarction has been intensively studied.[7 8] This study investigates the serial changes in conventional 12 lead electrocardiograms during acute myocardial infarction. It compares the functional electrophysiological changes in controls with the changes in those who have obtained coronary artery reperfusion after thrombolytic treatment. The aim was to investigate, by using the admission electrocardiogram as an index of myocardial injury, whether there is a predictable

Requests for reprints to Dr K J Hogg, Department of Materia Medica, Stobhill General Hospital, Glasgow G21 3UW.

Accepted for publication 16 February 1989

reduction in the electrocardiographic indices of myocardial infarct size in patients in whom reperfusion was successful.

Patients and methods

We studied three groups of patients. All groups entered the study within six hours of the onset of cardiac pain and had confirmatory electrocardiographic evidence of acute anterior myocardial infarction (ST elevation ≥ 1 mm in the standard leads 1 and aVL or 2 mm ST elevation in at least two precordial leads). Patients were excluded if they had sustained a previous myocardial infarction or had electrocardiographic changes that invalidated ST segment and Q wave analysis, including bundle branch block or pacemaker dependence.

Group 1 were historical controls who sustained an acute anterior myocardial infarction, but received no treatment other than conventional analgesia. They were admitted to our coronary care unit (from 1976 to 1979) before the introduction of routine thrombolytic treatment. All patients had prospective forms filled out detailing patient identification, clinical features on presentation, examination findings, treatment administered, and final diagnosis. These data were recorded on punch cards and stored in a mainframe computer. All electrocardiographic and haemodynamic tracings performed were stored separately as hard copy. This control group had no complications requiring specific cardioactive agents and had not received routine administration of any drugs that might influence myocardial infarct size—specifically β blockers, calcium channel blockers, or nitrates. The electrocardiographic changes measured therefore represent those occurring in a patient group with acute anterior myocardial infarction without cardiogenic shock or haemodynamic decompensation.

Group 2 consisted of patients who received thrombolytic treatment with the agent of our current thrombolysis protocol. Both groups are similar with respect to age, sex, and time to presentation (table 1). Exclusion criteria for patients receiving thrombolytic treatment were: a history of bleeding diathesis; a recent cerebrovascular accident (≤ 6 months); peptic ulceration; severe renal or hepatic disease; severe hypertension.

Patients in group 2 received either intracoronary streptokinase (250 000–500 000 units over 1 h n = 13) or an intravenous bolus dose of 30 mg anistreplase (n = 20). Coronary artery patency was determined by selective coronary arteriography, performed during treatment when intracoronary streptokinase was given 60–90 minutes after administration of intravenous anistreplase. The coronary arteriograms were read independently by two of the hospital clinicians who were not participating in the study. The patency of the infarct related vessel was decided and presence or absence of reperfusion was established. It was considered unethical to perform emergency angiography in the group 1 patients who received only opiate analgesia, and therefore the incidence of coronary artery patency at time of admission and of spontaneous reperfusion is unknown.[9]

Group 3 consisted of 22 patients (19 men, three women, age range 32–69, mean age 54 years) receiving either 1·5 megaunits intravenous streptokinase over 1 h or 30 mg intravenous anistreplase over five minutes. Reperfusion was assessed angiographically at 90 minutes after the start of treatment in all cases.

ELECTROCARDIOGRAPHIC ANALYSIS

After admission to the coronary care unit, 12 lead electrocardiograms were obtained on a Hewlett Packard Cardiograph 4700A. The chest lead positions were marked to ensure reproducibility. The ST segment area was calculated for each lead showing ST elevation (1 mm in the limb leads or 2 mm in the precordial leads taken at the J point) and measured as the area above the isoelectric line from the J point to the end of the T wave. The scores for all leads were summed as an index of myocardial injury or ischaemia, reflecting potential infarct size.

A second electrocardiogram was taken at 48 hours after the onset of symptoms and the evolved infarct size was measured by the QRS scoring system developed by Wagner *et al*[10] and further assessed in postinfarction patients by Palmeri *et al*.[11] This QRS scoring system is based on a 29 point system that depends upon the duration of R and Q waves and the ratios of R/S and R/Q amplitudes. A good correlation between anatomical anterior infarct size and this QRS score has been shown[12] and Palmeri *et al* showed an inverse correlation between the QRS score and left ventricular ejection fraction measured by radionuclides.[11] The higher the QRS score, the more extensive the infarct; a small QRS score indicates a limited infarct.

Table 1 *Data on study groups*

		Sex		*Mean age*		*Mean time to*
	No	*M*	*F*	*(y)*	*Treatment*	*presentation*
Group 1	35	29	6	55 5	Control (n = 35)	
Group 2	33	22	11	57 3	IC streptokinase (n = 13)	3 h 28 min (96 min)
					IV anistreplase (n = 20)	2 h 40 min (87 min)

IC, intracoronary; IV, intravenous.

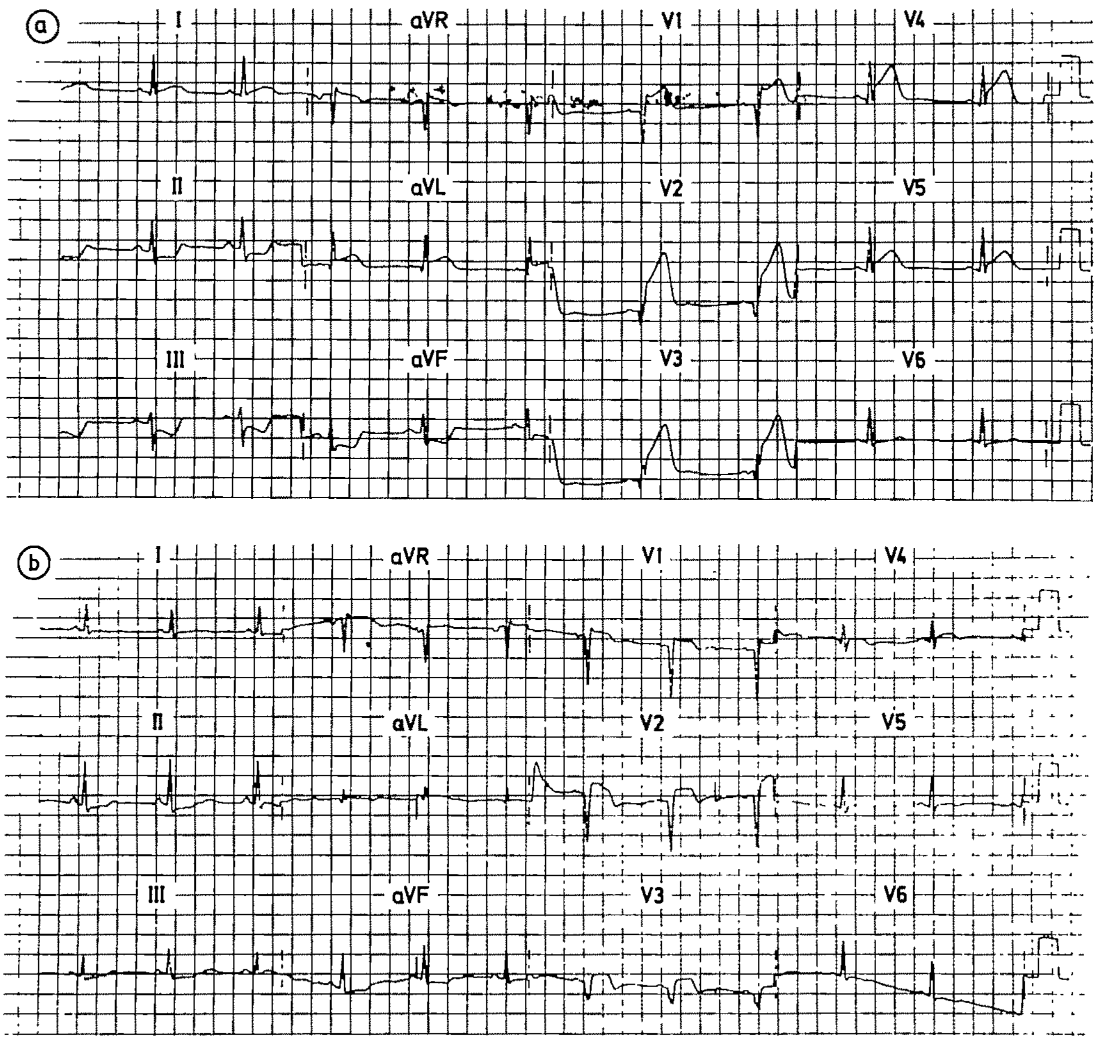


Fig 1 *(a) Electrocardiogram of a patient with acute anterior myocardial infarction who was admitted within 2 h 25 min after onset of pain (Σ ST area = 218 mm^2). (b) Same patient 48 hours after admission, after successful thrombolytic reperfusion. The QRS score is 3.*

STATISTICAL ANALYSIS

We used Student's unpaired *t* test to compare groups. Linear regression was performed with a statistical package on a Nodecrest computer, and an F test was applied to test the regression lines. Prediction intervals of QRS scores for future patients were calculated on the basis of data from the known data on patients showing reperfusion. This predicts the QRS score that would be expected had reperfusion occurred.

Results

Figures 1a and 1b show a representative electrocardiograph on admission and at 48 hours from which the $\sum$ ST segment area and the QRS scores were calculated. The degree of evidence of ischaemia on the electrocardiogram at presentation was similar in both groups ($\sum$ST area—group 1, 115 (60) mm^2; group 2, 126 (77) mm^2). This indicates that both groups had comparable myocardial ischaemia and

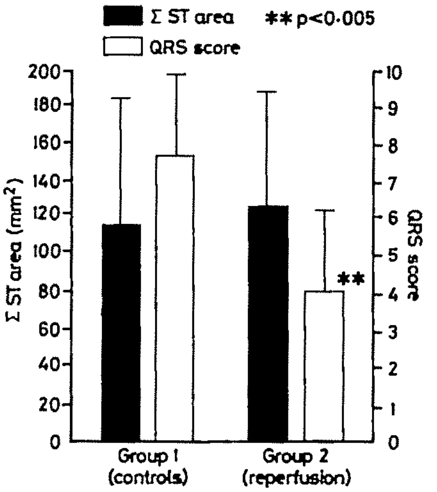


Fig 2 *Relation between Σ ST area (mean (SD)) on presentation and subsequent QRS score in group 1 (controls) and group 2 (reperfusion). There is a significant reduction in the QRS score in patients achieving reperfusion.*

potential infarct size. Of the patients in group 2, who received thrombolytic treatment, 11/13 receiving intracoronary streptokinase achieved successful reperfusion and 19/20 receiving intravenous anistreplase were found at angiography to have a patent infarct related vessel (left anterior descending). At 48 hours the evolved infarct size as assessed by the QRS score was significantly lower in those patients in whom reperfusion was obtained than for the control group (4·1 (2·5) compared with 7·8 (2·6)) ($p < 0·01$). Figure 2 shows the relation between myocardial ischaemia at admission ($\sum$ ST area) and eventual infarct size for both the control group and those patients achieving reperfusion.

Only three patients in group 2 did not show reperfusion and therefore we did not do a formal statistical analysis to compare the electrocardiographic score of the reperfusion group with the non-reperfusion group. The non-reperfused patients, however, showed Q wave development similar to the control group (table 2). The patients in group 2 were further divided according to the interval between the onset of cardiac pain and the time to thrombolytic treatment: group 2a ≤ 3 h (n = 16), group 2b > 3 h but ≤ 6 hours (n = 14). The values at presentation for $\sum$ ST segment area were 142 (82) mm² and 107 (70) mm² respectively (NS). The evolved infarct size scores were not significantly different for the two groups (group 2a, 4·2 (2·8); group 2b, 4·1 (2·1).

Table 2 *Mean values and standard deviations for Σ ST area and QRS scores for groups 1 and 2*

	Group 1 (Control)	Group 2	
		Reperfusion	Non-reperfusion
	n = 35	n = 30	n = 3
Σ ST area	115 (60)	126 (77)	279 (44 7)
QRS score	7·8 (2·6)	4·1 (2·5)	7·3 (4 5)

Figure 3 shows a scatter diagram of the individual scores for group 1 and group 2 with the respective linear regressions (QRS = 4·6 + 0·027 × $\sum$ ST area, and QRS = 1·6 + 0·020 × $\sum$ ST area). These regressions describing each group separately fit the data better than a single regression through all points ($p < 0·05$).

The 95% prediction intervals for QRS scores were calculated using the reperfusion data for group 2. These intervals are shown in fig 4 with control data for group 1 superimposed. Many control patients (51%) had QRS scores within the 95% prediction intervals for reperfused cases.

To investigate whether these intervals could be used accurately to predict QRS scores in individual patients, group 3 was used as a test group. The intervals were used to predict the QRS scores expected if reperfusion had occurred in the new patients. Out of 22 patients given thrombolytic treatment, 11 obtained a patent artery 90 minutes after treatment, and 11 did not. Both subgroups had similar degrees of myocardial injury on presentation ($\sum$ ST area = 147 (74) mm² (reperfusion group) and 171 (76) mm² (non-reperfusion group) (NS). Patients who obtained reperfusion had lower QRS scores than the group who did not (4·5 (3·1) *v* 9·3 (3·4)) ($p < 0·01$). Figure 5, however, shows that only five of the 11 without reperfusion had values outside the prediction intervals for reperfused cases. All patients except one who achieved reperfusion fall within the prediction intervals shown. The wide interindividual variability does not allow the prediction of a QRS score for an individual.

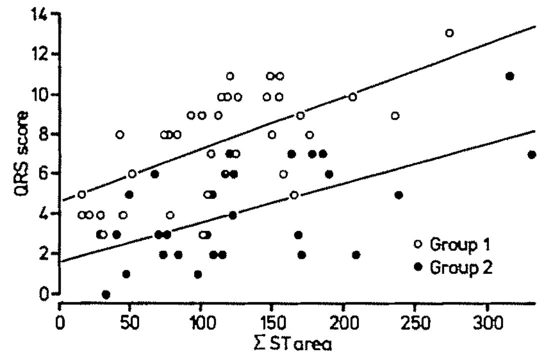


Fig 3 *Scatter diagram with individual scores for group 1 and group 2 showing lines of linear regression for each group.*

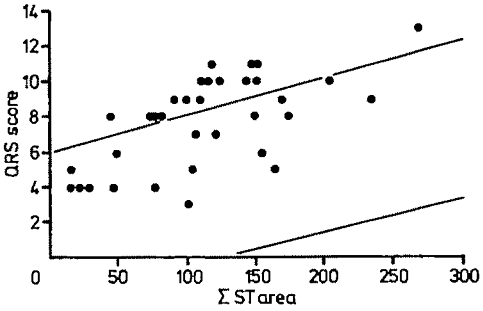


Fig 4 *95% prediction intervals for QRS scores for patients achieving successful reperfusion. The results for group 1 (controls) are superimposed.*

Discussion

This study shows that the sequential electrocardiographic changes are reduced in patients with acute anterior myocardial infarction who achieve coronary artery reperfusion after thrombolytic treatment. We studied whether this reduction in electrocardiographic infarct size could be used to predict individual QRS scores after reperfusion.

This was not a randomised study, but the control and intervention groups show similar distributions for sex, age, and time of presentation and similar values of ST elevation at presentation. Patients in the control group were not taking any drugs that could have influenced myocardial infarct size itself, and patients with cardiogenic shock or cardiac failure were also excluded. Selection for this group was therefore biased against inclusion of clinical subsets that may have had major myocardial damage. The electrocardiographic changes shown in this group therefore are the true natural course of acute anterior myocardial infarction. Because we considered it unethical to perform angiography in patients not being treated with thrombolysis, the control group may include patients with a subtotal coronary artery occlusion at the time of presentation or those who had spontaneous reperfusion.[9] Such coronary artery morphology may be associated with less eventual myocardial damage, and the inclusion of such individuals would again tend to bias results against finding a difference in evolved QRS scores.

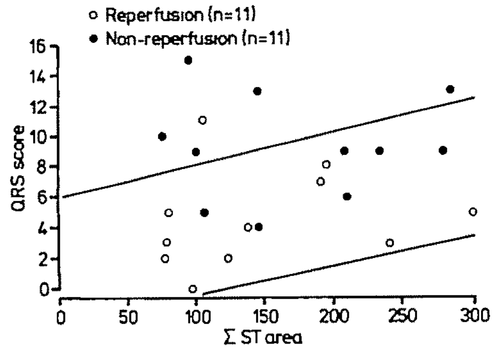


Fig 5 *Results of Σ ST area and QRS scores for group 3.*

It has long been recognised that ST segment elevation is an electrocardiographic marker of coronary artery occlusion.[13] The conventional 12 lead electrocardiogram has been used principally for diagnosis, but some studies have followed the natural course of the sequential changes that occur during infarction.[7,8] Selwyn *et al* showed that in patients with acute anterior myocardial infarction the precordial area of ST segment elevation at two hours was directly related to the extent of developed Q waves at 24 hours after the onset of pain.[8] An arbitrary time interval of 48 hours from presentation was chosen for the measurement of evolved infarct size in our study because Q wave development is believed to be complete at this time. Interventions such as intra-aortic balloon pumping[14] and administration of atenolol[15] and hyaluronidase,[16] designed to improve coronary artery perfusion and limit the degree of myocardial damage, have made use of changes in ST segments to indicate reduced ischaemia, and have used preservation of the R wave and reduction in Q wave development to indicate salvaged myocardium. We have already reported elsewhere on the specificity of ST segment reduction to predict coronary artery reperfusion during thrombolysis.[6,17] This present study investigated the association of ST segment elevation on admission with the use of subsequent evolved QRS score in patients with acute myocardial infarction as an indicator of vessel patency.

Animal studies with an epicardial mapping system have shown a convincing correlation between ST segment changes, subsequent Q wave development, myocardial creatine phosphokinase release, and histological evidence of necrosis.[18] However, opinion is divided on the ability of ST segment elevation to predict either the severity or the extent of myocardial necrosis in humans. Precordial mapping techniques in patients with acute myocardial infarction found little relation between ST segment elevation and subsequent infarct size as assessed by creatine phosphokinase release.[19,20] Problems can arise because coronary artery occlusion is not the only stimulus to affect the ST segment: pericarditis[21] and hyperkalaemia[22] may confuse the picture. Nevertheless, Askenazi *et al* reported that there is a predictable distribution of leads with ST elevation that ultimately develop signs of necrosis, and they suggested that a reduction in Q wave development would be of value in monitoring treatment designed to preserve myocardium.[7] This has been confirmed in similar work by Yusuf *et al.*[23]

Our present study confirms that a reduction in Q wave formation was associated with coronary artery reperfusion and that the reperfusion group had lower QRS scores than the control group. This is in contrast with the findings of Mikell *et al* who found that the QRS scores were the same irrespective of whether the patient had achieved successful reperfusion.[24] Mikell *et al* did show an improvement in left ventricular ejection fraction if the patient had reperfusion, and they suggested that there was a lag between electrocardiographic changes and left ventricular recovery or function. In the patients that they studied there was a preponderence of inferior infarctions, and this may explain why a difference in QRS score was not seen. Previous studies have shown that both ST segment changes and QRS scores are more variable in patients with inferior infarcts. This may reflect the small number of leads that show changes with inferior infarction, and that therefore represent only a limited proportion of the underlying myocardium.[25]

Despite being able to show a reduction in QRS scores in these patients in whom there was reperfusion, when prediction intervals were calculated for this group the limits were so wide and overlap between groups such that clinical predictions regarding infarct size were not helpful. There may be several reasons for this degree of inter-individual variability. Hackworthy *et al* used the same QRS score as we did and showed that collateral formation resulted in a smaller than expected infarct size.[26] Only in patients with a totally occluded artery with no collaterals did the initial peak ST elevation correlate with electrocardiographic infarct size. Certainly the presence of collaterals may reduce the expected QRS score in patients with no anterograde flow, who would be classed as not having reperfusion. We know from De Wood *et al* that 15% of patients presenting within six hours of infarction will have a subtotal occlusion, and that there is a spontaneous reperfusion rate.[9] Huey *et al* confirmed that patients with a naturally high patency rate at 10–13 days after infarction had better left ventricular function and less development of Q waves.[27] Similarly, Hackworthy *et al* showed a reduction in the expected QRS scores if there was a subtotal occlusion.[26]

It is not clear if the reduction in mortality in patients given thrombolytic treatment up to 24 hours after onset of symptoms[5,28,29] can be attributed to improvement in left ventricular function. Most studies that measure left ventricular function show benefit only if treatment is started in the first few hours.[30,31] In the present study beneficial changes in electrocadiographic indices of myocardial infarct size were shown even in those individuals given thrombolytic treatment 3–6 hours after the onset of symptoms. This suggests that functional benefit measured electrocardiographically may still be obtained if treatment can be started within six hours of the onset of cardiac pain. The potential for benefit may be present in those patients in whom coronary collaterals have previously developed or in whom acute infarction is associated with a subtotal coronary artery stenosis rather than a complete occlusion.[32]

We used conventional 12 lead electrocardiograms to show a significantly lower QRS score for the evolved infarct in patients who achieved reperfusion after thrombolysis for acute anterior myocardial infarction. Beneficial changes in this functional marker were obtained after successful reperfusion achieved by thrombolysis up to six hours from onset of pain. The wide inter-individual variability in QRS scores makes prediction of infarct size on an individual basis unhelpful. This variability may be accounted for in part by degree of collateral supply, time to reperfusion, or by the presence of a subtotal occlusion at time of presentation. None the less, the reduction in QRS scores seen in patients who achieve reperfusion after thrombolytic treatment may provide a non-invasive index of myocardial salvage for groups of patients.

We thank Beecham Pharmaceuticals for supplies of anistreplase.

References

1 Anderson JL, Marshall HW, Bray BE, *et al.* A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. *N Engl J Med* 1983;**308**:1312–8.

2 Kennedy JW, Ritchie JL, Davis KB, Stadius ML, Maynard C, Fritz JK. The Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. *N Engl J Med* 1985;**312**:1073–8.

3 Reduto LA, Smalling RW, Freund GC, Gould KL. Intracoronary infusion of streptokinase in patients with acute myocardial infarction: effects of reperfusion on left ventricular performance. *Am J Cardiol* 1981;**48**:403–9.

4 GISSI Study Group. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;**i**:397–401.

5 ISIS-2 Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both; or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;**ii**:349–60.

6 Hogg KJ, Hornung RS, Howie CA, Hockings N, Dunn FG, Hillis WS. Electrocardiographic prediction of

coronary artery patency following thrombolytic treatment in acute myocardial infarction: use of the ST segment as a non-invasive marker. *Br Heart J* 1988;**60**:275–80.

7 Askenazi J, Maroko PR, Lesch M, Braunwald E. Usefulness of ST segment elevations as predictors of electrocardiographic signs of necrosis in patients with acute myocardial infarction. *Br Heart J* 1977;**39**: 764–70.

8 Selwyn AP, Fox K, Welman E, Shillingford JP. Natural history and evaluation of Q waves during acute myocardial infarction. *Br Heart J* 1978;**40**:383–7.

9 De Wood MA, Spores J, Notske R, *et al.* Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med* 1980;**303**:897–902.

10 Wagner GS, Freye CJ, Palmeri ST, *et al.* Evaluation of a QRS scoring system for estimating myocardial infarct size. I Specificity and observer agreement. *Circulation* 1982;**65**:342–7.

11 Palmeri ST, Harrison DG, Cobb FR, *et al.* A QRS scoring system for assessing left ventricular function after myocardial infarction. *N Engl J Med* 1982; **306**:4–9.

12 Ideker RE, Wagner GS, Ruth WK, *et al.* Evaluation of a QRS scoring system for estimating myocardial infarct size. II Correlation with quantitative anatomic findings for anterior infarcts. *Am J Cardiol* 1982; **49**:1604–14.

13 Pardee HEB. An electrocardiographic sign of coronary artery obstruction. *Arch Intern Med* 1920;**26**:244–57.

14 Leinbach RC, Gold HK, Harper RW, Buckley MJ, Austen WG. Early intra-aortic balloon pumping for anterior myocardial infarction without shock. *Circulation* 1979;**58**:204–10.

15 Yusuf S, Ramsdale D, Peto R, *et al.* Early intravenous atenolol treatment in suspected acute myocardial infarction[Abstract]. *Lancet* 1980;**ii**:273–6.

16 Maroko PR, Hillis LD, Muller JE, *et al.* Favourable effects of hyaluronidase on electrocardiographic evidence of necrosis in patients with acute myocardial infarction. *N Engl J Med* 1977;**296**:898–903.

17 Hogg KJ, Hornung RS, Hockings S, Dunn FG, Hillis WS. ST segment analysis as a non invasive predictive indicator of coronary artery reperfusion in acute myocardial infarction [Abstract]. *Eur Heart J* 1985; **6**(suppl 1):16.

18 Hillis LD, Askenazi J, Braunwald E. Use of changes in the epicardial QRS complex to assess interventions which modify the extent of myocardial necrosis following coronary artery occlusion. *Circulation* 1976;**54**:591–8.

19 Norris RM, Barratt-Boyes C, Heng MK, Singh BN. Failure of ST segment elevation to predict severity of acute myocardial infarction. *Br Heart J* 1976;**38**: 85–92.

20 Thompson PL, Katavatis V. Acute myocardial infarction: evaluation of praecordial ST segment mapping. *Br Heart J* 1976;**38**:1020–4.

21 Thadani V, Chopra MP, Aber CP, Portal RW. Pericarditis after acute myocardial infarction. *Br Med J* 1971;**ii**:135–7.

22 Levine HD, Wanzer SH, Merrill JP. Dialysable currents of injury in potassium intoxication resembling acute myocardial infarction or pericarditis. *Circulation* 1956;**13**:29–36.

23 Yusuf S, Lopez R, Maddison A, *et al.* Value of electrocardiogram in predicting and estimating infarct size in man. *Br Heart J* 1979,**42**:286–93.

24 Mikell FL, Petrovich J, Snyder MC, *et al.* Reliability of Q wave formation and QRS score in predicting regional and global left ventricular performance in acute myocardial infarction with successful reperfusion. *Am J Cardiol* 1986;**57**:923–6.

25 Savage RM, Wagner GS, Ideker RE, Podolsky SA, Hackel DB. Correlation of post mortem findings with electrocardiographic changes in patients with myocardial infarction. *Circulation* 1977;**55**:279–85.

26 Hackworthy RA, Vogel MB, Harris PJ. Influence of infarct artery patency on the relation between initial ST segment elevation and final infarct size. *Br Heart J* 1986;**56**:222–5.

27 Huey BL, Gheorghiade M, Crampton RS, *et al.* Acute non-Q wave myocardial infarction associated with early ST segment elevation: evidence for spontaneous coronary reperfusion and implication for thrombolytic trials. *J Am Coll Cardiol* 1987;**9**:18–25.

28 Stampfer MJ, Goldhaber SZ, Yusuf S, Peto R, Hennekens CH. Effect of intravenous streptokinase on myocardial infarction. *N Engl J Med* 1982; **307**:1180–2.

29 Yusuf S, Collins R, Peto R, *et al.* Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: overview of results on mortality, reinfarction and side-effects from 33 randomised controlled trials. *Eur Heart J* 1985;**65**:556–85.

30 Sheehan FH, Mathey DG, Schofer J, *et al.* Effect of intervention in salvaging left ventricular function in acute myocardial infarction—a study of intracoronary streptokinase. *Am J Cardiol* 1983;**52**:431–8.

31 Ritchie JL, Cerqueira M, Maynard C, Davis IC, Kennedy JW. Ventricular function and infarct size: The Western Washington Intravenous Streptokinase in Myocardial Infarction Trial. *J Am Coll Cardiol* 1988;**11**:689–97.

32 Rogers WT, Hood WP, Mantle JA, *et al.* Return of left ventricular function after reperfusion in patients with myocardial infarction: importance of subtotal stenoses or infarct collaterals. *Circulation* 1984; **62**:338–49.

Br Heart J 1989;61:496–501

Silent myocardial ischaemia in patients referred for coronary bypass surgery because of angina: a comparison with patients whose symptoms were well controlled on medical treatment

DAVID MULCAHY, JENNIFER KEEGAN, DAVID LINDSAY, JANE SPARROW, AMANDA PARK, CHRISTINE WRIGHT, KIM FOX

From the National Heart Hospital, London

SUMMARY The frequency and characteristics of silent ischaemia were prospectively studied in 114 patients with confirmed coronary artery disease and angina. Fifty seven patients who had angina that was not adequately controlled by standard medications were referred for elective coronary artery bypass surgery (group 1). Fifty seven other patients had symptoms that were well controlled on medical treatment (group 2). Patients underwent treadmill exercise testing ($n = 109$) and 48 hours of ambulatory ST segment monitoring (total 5125 hours). Patients in group 1 had more severe coronary artery disease and a shorter time to 1 mm ST segment depression and maximal exercise. Twenty two patients in group 1 (38%) and 16 in group 2 (28%) had $\geqslant 1$ episode of silent ischaemia during 48 hours of ST monitoring. There was no significant difference in the mean frequency of silent ischaemic episodes in 24 hours between the two groups (group 1 0·72 *v* group 2 0·64); however, the mean frequency of painful ischaemic episodes in 24 hours was greater in group 1 patients (0·51) than in group 2 (0·11). In both groups the frequency of silent ischaemia was significantly related to a positive exercise test, as was the total duration of silent ischaemia. The circadian variation of silent ischaemia showed a peak of episodes in the evening in both groups.

The frequency of silent ischaemia in patients with coronary artery disease and angina receiving standard antianginal medications was not related to the severity of symptoms, but was significantly related to a positive exercise test. Thirty three percent of the patients studied had evidence of silent ischaemia during 48 hours of ambulatory ST segment monitoring; however, only four patients (3·5%) had frequent ($\geqslant 5$) daily episodes of silent ischaemia.

The introduction of ambulatory ST segment monitoring has allowed us to study patients with coronary artery disease and angina during their daily lives, and it has been shown that ST segment change, the electrocardiographic hallmark of ischaemia, occurs in the absence of angina or its equivalents in most cases.[1-3] ST segment change represents true ischaemia in patients with coronary artery disease.[4 5] Acute myocardial infarction occurs without symptoms in about 25% of cases,[6] and the prognosis is as serious as that of myocardial infarction accompanied by pain. Because there is concern that silent myocardial ischaemia may be causally related to acute myocardial infarction[7] and sudden death,[8] it has been proposed that we should investigate patients for the presence of silent ischaemia and treat all ischaemia. Many investigators have established the frequency and characteristics of silent ischaemia; however, such studies have included patients not taking routine antianginal medications.[1 3 9] But most patients with confirmed coronary artery disease and angina usually receive antianginal treatment. Investigation of patients in this setting may be more relevant to assessing silent myocardial ischaemia in clinical practice.

We studied 114 patients with confirmed coronary artery disease and varying degrees of angina who

Requests for reprints to Dr David Mulcahy, National Heart Hospital, Westmoreland Street, London W1M 8BA.

Accepted for publication 31 January 1989

were receiving standard antianginal medications, firstly, in order to investigate whether the frequency of silent ischaemia is related to the level of symptoms and, secondly, to establish the frequency and characteristics of silent ischaemia in patients with coronary artery disease receiving standard antianginal treatment.

Patients and methods

One hundred and fourteen patients (101 men) aged 30–74 years (mean 55·5 years) with proven coronary artery disease (21 single, 44 two vessel, 49 three vessel disease) and angina were studied between May 1987 and May 1988 to establish the relation between silent myocardial ischaemia and symptoms. We graded angina according to the classification of the Canadian Cardiovascular Society.[10] Group 1 consisted of 57 patients who, despite adequate antianginal therapy, had poorly controlled anginal symptoms (grade III/IV) and were referred for elective coronary artery bypass surgery. Group 2 consisted of 57 patients whose angina was well controlled on standard antianginal treatment (grade I/II) and were due for further review as outpatients in six months to one year. Inclusion criteria included the presence of clinically significant coronary artery disease and angina that required regular antianginal medication. We excluded patients taking medication known to affect the ST segment, those with significant conduction disorders, and patients referred for surgery primarily for prognostic rather than symptomatic reasons.

All patients underwent cardiac catheterisation by either the Judkins or the Sones technique. All angiograms were independently reported by one of two radiologists. A significant stenosis was taken to be a ⩾70% reduction in luminal diameter of a major vessel.

AMBULATORY ST SEGMENT MONITORING

For ambulatory ST segment monitoring we used pregelled electrodes to record two bipolar leads, an anterior lead (CM5), and an inferior lead. The sites and methods of application of these electrodes have been described elsewhere.[11] Two channel recordings were then obtained on magnetic tape by a frequency modulated dual channel recorder (Oxford Medilog 2, frequency response 0·05–40 Hz). All tapes were visually analysed at 60–120 times normal speed by an Oxford Medilog MA 20 analyser, and all printouts were recorded at 25 mm/s. Significant ST segment depression was defined as planar or downsloping ST segment shift of ⩾1 mm measured 0·08 s after the J point and persisting for more than one minute. Significant ST segment elevation was defined as an upward shift of the ST segment of ⩾1 mm at the J point compared with the resting recording. Changes in the T wave vector were not regarded as evidence of myocardial ischaemia unless they were accompanied by significant ST segment changes.

All ambulatory monitoring was performed outside hospital after each patient had been referred either for elective surgery or for routine outpatient follow up. All patients were encouraged to continue with their normal daily activities. During the period of monitoring, patients kept a detailed angina diary, recording the time of each episode of pain, the activity at the onset of symptoms, and the requirement for glyceryl trinitrate. They pressed an event marker on the ambulatory monitor at the onset of symptoms.

TREADMILL EXERCISE TESTING

One hundred and nine patients underwent maximal symptom limited treadmill exercise testing according to the modified Bruce protocol. Electrocardiograms were recorded at the start of exercise and every three minutes of exercise, and whenever chest pain, hypotension, or significant ST depression developed. A test was regarded as positive if there was ST segment depression of ⩾1 mm that was planar or downsloping 0·08 s after the J point. Exercise was limited by the development of chest pain, dyspnoea, exhaustion, intermittent claudication, complex ventricular arrhythmias, or hypotension.

ANTIANGINAL MEDICATIONS

All patients were taking routine antianginal medications at the time of investigation. Thirty two patients were on one drug (18, β blocker; 12, calcium antagonist; and two, nitrate); 52 were on two drugs (28, β blocker + calcium antagonist; 15, β blocker + nitrate, and nine, calcium antagonist + nitrate). A further 30 patients were receiving a β blocker, calcium antagonist, and nitrate. All patients were also taking short acting nitrates as required.

STATISTICAL ANALYSIS

We compared the frequency and duration of ischaemic episodes with other variables within groups 1 and 2 by the Mann-Whitney U test, and variables between groups 1 and 2 by the t test or the Mann-Whitney U test as appropriate. A p value of $<0·05$ was regarded as significant. A two harmonic Fourier fit was applied to the hourly frequencies of silent ischaemia.

Results

The two groups were similar for mean age (group 1

56·5 *v* group 2 54·5 years) and male sex (group 1 53 *v* group 2 48), and had a similar number of positive exercise tests (group 1 39 *v* group 2 30) and hours of ST segment monitoring (group 1 2564 *v* group 2 2561 hours). There was no significant difference between groups in terms of previous myocardial infarction, history of smoking, hypertension, diabetes, or a family history of coronary artery disease. All patients in group 1 had grade III (n = 32) or grade IV (n = 25) angina, and those in group 2 had grade I (n = 30) or grade II (n = 27) angina. Table 1 shows the degree of coronary artery disease, the exercise test, and the antianginal medications taken by the two groups. Group 1 patients had more severe coronary artery disease (p < 0·001) and a shorter time to pain (p < 0·001). ST segment depression (p < 0·001), and maximal exercise (p < 0·001) on treadmill exercise testing. Although the number of routine antianginal medications taken by group 1 patients (2·09) was not different from that of group 2 patients (1·86) (p = 0·09), group 1 patients were more likely to be taking combination treatment (p < 0·05).

AMBULATORY MONITORING DATA

A total of 38 patients (33%) had 154 episodes of silent ischaemia during 5125 hours of ambulatory monitoring. Table 2 shows the findings on ambulatory ST segment monitoring in the two groups. There was no significant difference between groups in the mean frequency of silent ischaemic episodes per 24 hours or their total duration. The mean frequency of painful ischaemia in 24 hours was significantly greater in group 1 patients (group 1 0·52 *v* group 2 0·11, p < 0·01), as was the mean frequency of pain without ST segment change (group 1 1·57 *v* group 2 0·98, p < 0·01).

Table 1 *Severity of coronary artery disease, exercise test, and number of antianginal medications in the two groups*

	Group 1 (n = 57)	*Group 2 (n = 57)*	*p*
Coronary artery disease:			
1 vessel	5	16	< 0·001
2 vessel	16	28	
3 vessel	36	13	
Exercise test			
Positive	39	30	NS
Negative	15	25	
Time to maximum exercise (min)	7·16	9·73	< 0·001
Time to 1 mm ST depression (min)	5·60 (n = 39)	8·08 (n = 30)	< 0·001
Time to pain (min)	5·53 (n = 46)	7·73 (n = 29)	< 0·001
Antianginal medications:			
Single	10	21	< 0·05
Multiple	46	36	

Table 2 *Mean number and duration of episodes of silent and painful ischaemia and mean number of episodes of pain without ST segment change in the two groups*

	Group 1 (n = 57)	*Group 2 (n = 57)*	*p*
Silent ischaemic episodes:			
Mean no/24 h	0·72	0·64	NS
Mean duration/24 h (min)	14·50	17·60	NS
Painful ischaemic episodes:			
Mean no/24 h	0·52	0·11	< 0·001
Mean duration/24 h (min)	10·50	3·95	< 0·01
Episodes of pain without ST segment changes:			
Mean no/24 h	1·57	0·98	< 0·01

There was no difference between groups in the mean duration of silent ischaemia per 24 hours (group 1 14·5 min *v* group 2 17·6 min, p = NS); however, the duration of painful ischaemia was significantly greater in group 1 (group 1 10·5 min *v* group 2 3·95 min, p < 0·01).

The number of patients with multiple daily episodes (≥5/day) of silent ischaemia was recorded (fig 1). Four patients (3·5%) had five or more episodes per day (two from group 1 and two from group 2). A further seven patients had more than two but less than five episodes per day. Ninety per cent of all patients had two or fewer episodes of silent ischaemia per day.

AMBULATORY MONITORING AND EXERCISE TESTING

One hundred and nine patients had an exercise test with which to compare the results of ambulatory monitoring. Figure 2 shows the relation between silent ischaemia on ambulatory monitoring and a

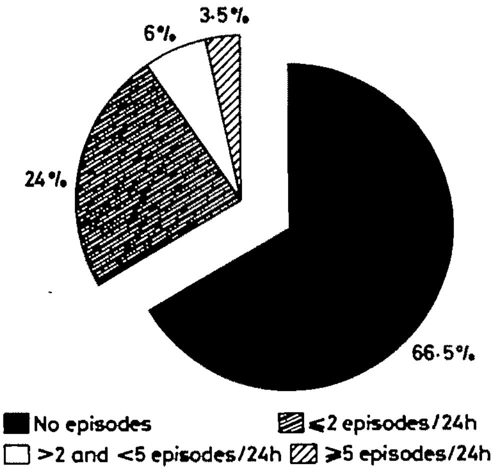


Fig 1 *Frequency of episodes of silent ischaemia per 24 hours in 114 patients on treatment.*

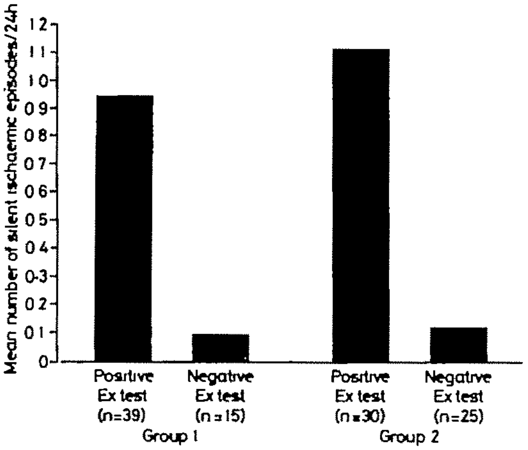


Fig 2 *Relation between the mean frequency of silent ischaemic episodes and a positive or negative exercise test in both groups.*

positive or negative exercise test in both groups. The presence of silent ischaemia was significantly related to a positive exercise test in both groups (p < 0·01, p < 0·01). The frequency of painful ischaemia was also related to a positive exercise test (p < 0·01), and such pain occurrred predominantly in the more symptomatic group 1 patients, who also developed angina significantly more frequently during exercise than group 2 patients (group 1 46 *v* group 2 29, p < 0·001). The mean duration of silent ischaemia over 24 hours was also related to a positive exercise test in both groups (group 1 positive test 19·4 min, negative test 1·9 min, p < 0·02; group 2 positive test 30·7 min, negative test 3·3 min, p < 0 01).

AMBULATORY MONITORING AND OTHER VARIABLES

There was no significant relation between the frequency of silent ischaemia and either the severity of coronary artery disease or the number of medications taken by the patients. Assessment of the circadian pattern of silent ischaemia in all 114 patients showed a primary peak of episodes in the evening and a secondary one in the morning (fig 3). Although we were unable to gain meaningful information on the effects of all combinations of medications on the circadian variation of silent ischaemic episodes because there were too few patients and ischaemic episodes, we were able to study the relation between the pattern of silent ischaemic episodes and use of β blockers, either alone or in combination (n = 91). Again this showed a primary peak in episodes in the evening.

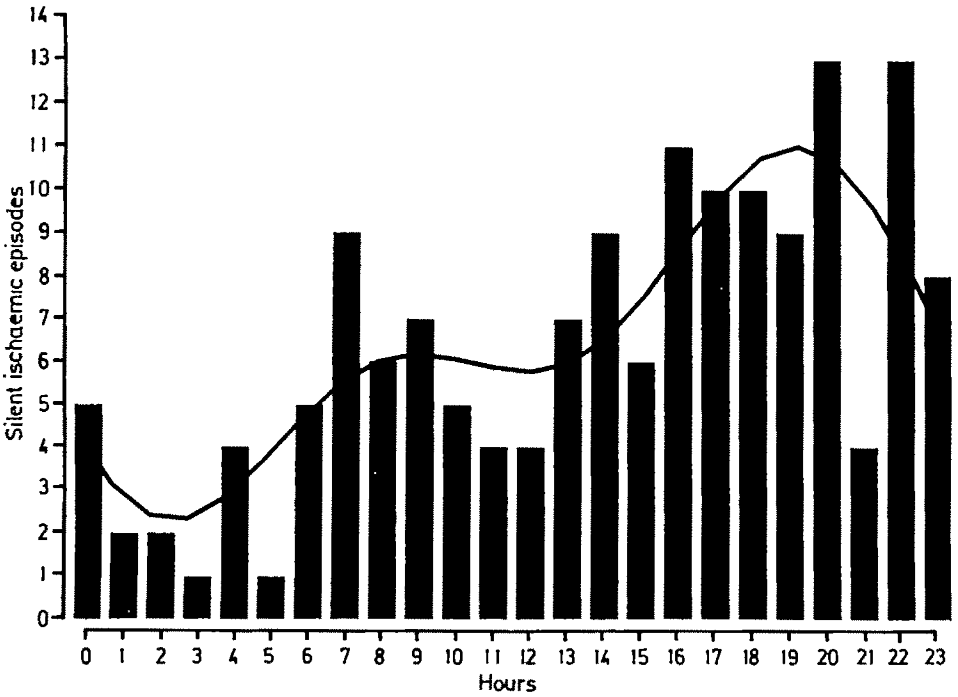


Fig 3 *Circadian pattern (with a bimodal fit superimposed) of silent ischaemic episodes in 114 patients on treatment.*

Discussion

Many workers who have defined the frequency and characteristics of silent myocardial ischaemia in patients with coronary artery disease have selected patients with a positive exercise test[1 9 12] or those who are not receiving routine antianginal treatment at the time of investigation.[1 3 9] This present study allows us to assess the frequency of silent ischaemia in an "unselected" group of symptomatic patients with significant coronary artery disease who were taking standard medications. This group of patients is more representative of a general population of patients with proven coronary artery disease and angina, most of whom are treated with antianginal medications.

We studied patients in two groups, defined by their angina symptoms according to the criteria of the Canadian Cardiovascular Society.[10] In those patients with symptoms that were poorly controlled on medical treatment, the ratio of silent to painful episodes (1·39:1) was much lower than in earlier reports,[1-3] whereas in those whose symptoms were well controlled on medical treatment the high ratio of silent to painful ischaemia persisted (5·65:1). Like Quyyumi *et al*[13] we found that a patient's symptoms did not relate to the frequency of silent ischaemia; however, we found that patients with inadequately controlled symptoms did have more painful ischaemia and more pain without ST segment change.

It is not clear why some patients seem to be less aware of their ischaemia, particularly in a study group such as this where all patients had anginal symptoms to a greater or lesser extent. Proposed theories include a generalised defective perception of painful stimuli,[14] altered sensibility to pain,[15] and a defective anginal warning system.[16] The explanation for the silent ischaemia in this group of patients is likely to be multifactorial. It is somewhat surprising that patients whose symptoms are well controlled have a similar amount of silent ischaemia to those who are restricted by symptoms and who have significantly worse exercise tests.[3] Perhaps patients who are less restricted by angina push themselves harder in their daily activities.

In an earlier study we found that about half of all patients with confirmed coronary artery disease had evidence of silent ischaemia on ambulatory monitoring when they were not taking routine antianginal treatment.[3] In the present study of patients with coronary artery disease and angina who were receiving standard antianginal treatment, one third had evidence of silent ischaemia on ambulatory monitoring; the mean frequency and total duration of silent ischaemia, however, were much reduced, as might be expected with the use of standard antianginal medications, which have been reported to be effective in reducing the frequency of silent ischaemia.[17] It remains to be established whether combination treatment is more beneficial than single drugs in treating silent ischaemia. Studies of larger numbers of patients should clarify this. Nor is it certain that silent ischaemia is associated with an adverse prognosis in patients with stable angina, or that medications affect that prognosis. A recent report has suggested that in patients with stable angina and a positive exercise test for ischaemia, the presence of silent ischaemia during ambulatory monitoring identifies a subgroup of patients at increased risk of an early unfavourable outcome.[18]

As in published reports[3 11 19] in patients who were not taking antianginal drugs we showed a relation between the frequency of silent ischaemia and a positive exercise test, irrespective of medications or the level of symptoms a patient suffers. This finding is important because it allows us to identify, by a standard investigation, patients at increased risk of having silent ischaemia during their daily lives, and also suggests that similar mechanisms underlie the development of ischaemia in the exercise and ambulatory setting.

We were unable to show any significant relation between the frequency of silent ischaemia and the severity of coronary artery disease in patients receiving treatment. This may have been because the numbers we studied were too small. In a previous study in patients with coronary artery disease not taking routine treatment there was a significant relation between the frequency of silent ischaemia and the severity of coronary disease; but only when those with three vessel and single vessel coronary disease were compared. Considerable overlap was noted between those groups with differing levels of coronary disease.[3]

Others reported a significant peak of silent ischaemic episodes in the morning waking hours when patients with coronary artery disease were not taking treatment.[20 21] This morning peak was confirmed for acute myocardial infarction.[22 23] We have previously shown that β adrenergic blockade eliminates the primary morning peak in episodes of silent ischaemia, with the primary peak occurring in the evening,[20] and β blockade has also been shown to eliminate the morning peak of acute myocardial infarction.[22 23] The circadian variation of silent ischaemic episodes in our present study group, who were taking standard antianginal treatment, corresponds closely to that previously shown for patients receiving a β blocking agent,[20] with the primary peak in episodes in the evening at a time when myocardial oxygen demand might be expected to be low. This pattern probably results from the fact that almost all patients were receiving a β blocker as part of their treatment, and suggests that patients on β blocking agents are less likely to develop silent ischaemia in the morning. The effects of various combination treatments on the circadian pattern of silent ischaemia still require elucidation.

The frequency of silent myocardial ischaemia in patients with coronary artery disease and angina who are receiving standard medical treatment is not related to the degree of symptoms that a patient suffers, though painful ischaemia is more common in those whose symptoms are inadequately controlled by medication. The frequency and total duration of silent and painful ischaemia are significantly related to a positive exercise test, suggesting similar pathophysiological mechanisms. In patients treated with β blockers, either alone or as part of combination treatment, the peak of silent ischaemic episodes occurs in the evening. We found that two thirds of patients with coronary artery disease and angina of varying severity receiving medical treatment had no silent ischaemia during 48 hours of ambulatory monitoring, and only 11 patients (9·6%) had more than two episodes of silent ischaemia a day.

We thank the British Heart Foundation for their support.

References

1 Cecchi AC, Dovellini EV, Marchi F, Pucci P, Santoro GM, Fazzini F. Silent myocardial ischaemia during ambulatory electrocardiographic monitoring in patients with effort angina. *J Am Coll Cardiol* 1983; 1:934–9.

2 Tzivoni D, Gavish A, Benhorin J, Karen A, Stern S. Myocardial ischaemia during daily activities and stress. *Am J Cardiol* 1986;58:47B–50B.

3 Mulcahy D, Keegan J, Crean P, *et al.* Silent myocardial ischaemia in chronic stable angina: a study of its frequency and characteristics in 150 patients *Br Heart J* 1988;60:417–23.

4 Deanfield JE, Selwyn AP, Chierchia S, *et al.* Myocardial ischaemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. *Lancet* 1983;i:753–8.

5 Levy RD, Shapiro LM, Wright C, Mockus LJ, Fox KM. The haemodynamic significance of asymptomatic ST.segment depression assessed by ambulatory pulmonary artery pressure monitoring. *Br Heart J* 1986;56:526–30.

6 Kannel WB, Abbott RD. Incidence and prognosis of unrecognised myocardial infarction. An update on the Framingham Study. *N Engl J Med* 1984;311:1144–7.

7 Assey ME, Walters GL, Hendrix GH, Carabello BA, Usher BW, Spann JF. Incidence of acute myocardial infarction in patients with exercise induced silent myocardial ischaemia. *Am J Cardiol* 1987;59: 497–500.

8 Sharma B, Asinger R, Francis GS, Hodges M, Wyeth RP. Demonstration of exercise induced painless myocardial ischaemia in survivors of out of hospital ventricular fibrillation. *Am J Cardiol* 1987;59:740–5.

9 Deanfield JE, Shea M, Ribiero P, *et al.* Transient ST segment depression as a marker of myocardial ischaemia during daily life. *Am J Cardiol* 1984; 54:1195–200.

10 Campeau L Grading of angina pectoris [Letter]. *Circulation* 1976;54:522–3.

11 Quyyumi AA, Mockus L, Wright C, Fox KM. Morphology of ambulatory ST segment changes in patients with varying severity of coronary artery disease. Investigation of the frequency of nocturnal ischaemia and coronary spasm. *Br Heart J* 1985;53: 186–93.

12 Cohn PF, Lawson WE. Characteristics of silent myocardial ischaemia during out-of-hospital activities in asymptomatic angiographically documented coronary artery disease. *Am J Cardiol* 1987;59:746–9.

13 Quyyumi AA, Wright CM, Mockus LJ, Fox KM. How important is a history of chest pain in determining the degree of ischaemia in patients with angina pectoris? *Br Heart J* 1985;54:22–6.

14 Glazier JJ, Chierchia S, Brown MJ, Maseri A. Importance of generalised defective perception of painful stimuli as a cause of silent myocardial ischaemia in chronic stable angina pectoris. *Am J Cardiol* 1986; 58:667–72.

15 Droste C, Roskamm H. Experimental pain measurements in patients with asymptomatic myocardial ischaemia. *J Am Coll Cardiol* 1983;1: 940–5.

16 Cohn PF. Silent myocardial ischaemia in patients with a defective anginal warning system. *Am J Cardiol* 1980; 45:697–701.

17 Frishman WH, Teicher M. Antianginal drug therapy for silent myocardial ischaemia. *Am Heart J* 1987; 114:140–7.

18 Rocco MB, Nabel EG, Campbell S, *et al.* Prognostic importance of myocardial ischaemia detected by ambulatory monitoring in patients with stable coronary artery disease. *Circulation* 1988;78:877–84.

19 Campbell S, Barry J, Rebecca GS, *et al.* Active transient myocardial ischaemia during daily life in asymptomatic patients with positive exercise tests and coronary artery disease. *Am J Cardiol* 1986;57:1010–6.

20 Mulcahy D, Keegan J, Cunningham D, *et al.* Circadian variation of total ischaemic burden and its alteration with anti-anginal agents. *Lancet* 1988;ii:755–9.

21 Rocco MB, Barry J, Campbell S, *et al.* Circadian variation of transient myocardial ischaemia in patients with coronary artery disease. *Circulation* 1987;75: 395–400.

22 Muller JE, Stone PH, Turi ZG, *et al.* Circadian variation in the frequency of onset of acute myocardial infarction. *N Engl J Med* 1985;313:1315–22.

23 Willich SN, Linderer T, Wegscheider K, Schroder R. Increased risk of myocardial infarction in the morning [Abstract]. *J Am Coll Cardiol* 1988;11:28A.

Br Heart J 1989;61:502–5

Initial experience with a microprocessor controlled current based defibrillator

G W N DALZELL, S R CUNNINGHAM, J ANDERSON,* A A J ADGEY

*From the *University of Ulster, Jordanstown, and Regional Medical Cardiology Centre, Royal Victoria Hospital, Belfast, Northern Ireland*

SUMMARY Intramyocardial current flow is a critical factor in successful ventricular defibrillation. The main determinants of intramyocardial current flow during transthoracic countershock are the selected energy and the transthoracic impedance of the patient. To optimise the success of the first shock and to titrate energy dosage according to each patient's transthoracic impedance, a microprocessor controlled current based defibrillator was developed. It was compared with a conventional energy based protocol of 200 J (delivered energy), 200 J, then 360 J if required in 42 consecutive episodes of ventricular fibrillation in 33 men and seven women. The mean (SD) predicted transthoracic impedance was 69·9 (14·0) Ω. First shock success with the standard protocol was 80·9%, and first or second shock success was 95·2%. The microprocessor controlled current based defibrillator automatically measured transthoracic impedance and calculated the energy required to develop a selected current in each patient. A current protocol of 30 A, 30 A, then 40 A, if required, was used in 29 men and 12 women with 41 episodes of ventricular fibrillation. Transthoracic impedance (mean 65·1 (15·9) Ω) was similar to that in the energy protocol group and success rates for first shock (82·9%) and first or second shocks (97·5%) were also similar. The mean delivered energy per shock with the current based defibrillator for first or second shock success was significantly less (144·8 J) with the energy protocol (200 J). The mean peak current of successful shocks was also significantly reduced (29·0 *v* 31·9 A).

A current based defibrillator titrates energy according to transthoracic impedance; it has a success rate comparable to conventional defibrillators but it delivers significantly less energy and current per shock.

Ventricular defibrillation is successful when a critical mass of myocardium is depolarised.[1] Although conventional defibrillators are calibrated in terms of energy, it has been suggested that current rather than energy is more important in correcting ventricular fibrillation.[2 3] Electrical countershock can be associated with adverse effects and ideally ventricular fibrillation should be terminated with a threshold shock. However, in humans it is not possible to determine the electrical threshold for transthoracic ventricular defibrillation. Nevertheless, the principle of giving the smallest effective electrical shock remains valid. The concept of advance prediction of transthoracic impedance[4] before defibrillator discharge suggested that it might be possible to develop a defibrillator that delivers a fixed current. We have developed a microprocessor controlled current based defibrillator and in this study we compared it with a standard energy based defibrillator.

Patients and methods

We studied two groups of consecutive patients who had ventricular fibrillation within or outside hospital. In all patients pre-gelled adhesive electrocardiographic defibrillator pads (12 cm diameter) were applied in the anteroapical position.

For the first 42 consecutive episodes of ventricular fibrillation in 40 (33 men, seven women) patients (mean age 61·5 years) we used a standard energy protocol of 200 J (delivered energy) for a first shock, followed by 200 J for a second shock if required and subsequent shocks of 360 J if necessary. Trans-

Requests for reprints to Dr A A J Adgey, Regional Medical Cardiology Centre, Royal Victoria Hospital, Belfast BT12 6BA, Northern Ireland

Accepted for publication 2 February 1989

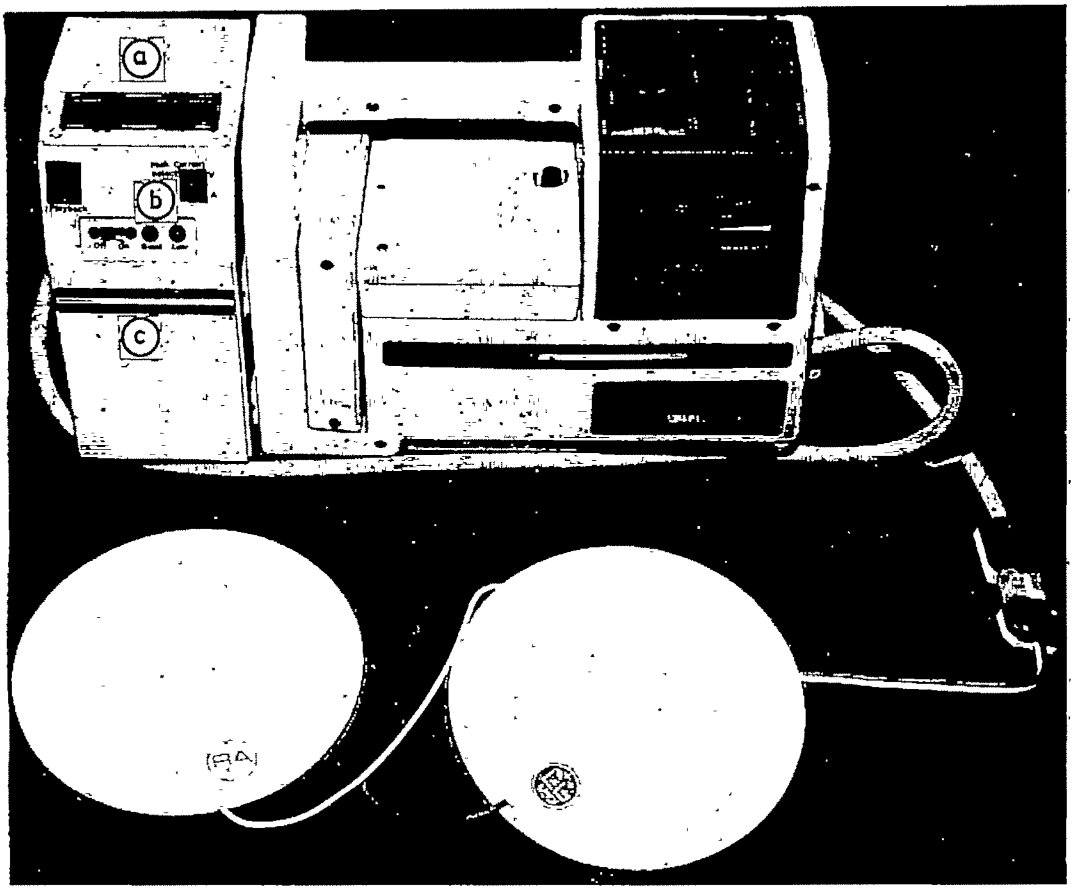


Fig 1 *Microprocessor based current defibrillator. The microprocessor and device for measuring transthoracic impedance is mounted behind a standard liteguard 6 defibrillator. (a) Digital display; (b) thumbwheel switch; (c) microprocessor.*

thoracic impedance was recorded immediately before defibrillator discharge by a 30 kHz low amplitude (100 μA) current applied via the electrode pads. We have previously shown that this method accurately predicts the actual transthoracic impedance to a defibrillatory shock, both in patients with atrial arrhythmias,[5] and ventricular fibrillation.[6] The peak transthoracic current generated by each discharge was also recorded for each shock.

In the next 41 consecutive patients with 41 episodes of ventricular fibrillation (29 men and 12 women, mean age 63·3 years) we used a microprocessor controlled current based defibrillator (fig 1). In a previous study that we performed in patients with ventricular fibrillation who were defibrillated by an energy protocol the mean peak current for successful defibrillation was 29·2 A.[6] So we decided to use 30 A for the initial shock in this study. If this was unsuccessful we used a second 30 A shock. Subsequent shocks were to be 40 A. The peak current (Is) was selected by means of a thumbwheel switch. The transthoracic impedance was automatically measured by a low amplitude high frequency current method described above. The microprocessor used the current selected, the predicted transthoracic impedance measurement, and pre-programmed defibrillator characteristics to "look-up" the energy required (Ed) to develop the current selected (Is). This energy level was digitally displayed. The defibrillator was then charged by the operator pressing the charge button and matching up the two energies that were displayed side by side on the digital display. This process occurred almost as soon as the charge button was pressed. There was good correlation between the energy required and delivered energy for each patient ($r = 0{\cdot}98$)

For each shock, the predicted transthoracic impedance, the required energy (Ed), the actual delivered energy (Ea), selected peak current (Is), and actual peak transthoracic current (Ip) were recorded in non-volatile memory and played back where required. The success or failure of each shock was recorded.

We then compared patients treated with the energy protocol with those treated by the current protocol. We analysed continuous variables (transthoracic impedance, peak current, energy) by Student's *t* test, and discrete variables such as defibrillation success by χ^2 and the fourfold table tests. Results are expressed as mean (1 SD).

Results

ENERGY PROTOCOL

The mean predicted transthoracic impedance for this group for first or second shocks was 69·9 (14·0) Ω (range 41 0–100·0 Ω). A single shock of 200 J was successful in 80·9% (34/42) of episodes and the cumulative success rate for two 200 J shocks was 95·2% (40/42). For successful 200 J shocks the mean peak current was 31·9 (5·7) A (range 21·8–46·6 A). This was significantly higher than that for unsuccessful 200 J shocks (28·4 (3·6) A, range 24·8–35·9) ($p < 0.05$).

CURRENT PROTOCOL

For successful shocks where the selected peak current (Is) was 30 A the mean actual peak current (Ip) was 29·0 (1·4) A (range 25·0–31·1 A). Thus the current based defibrillator accurately calculated the required energy to develop the preselected current of 30 A. This system accurately generated a constant current over a wide range of transthoracic impedances (fig 2).

The mean predicted transthoracic impedance of this group for first or second shocks was 65·1 (15·9) Ω (range 38·0–97·0 Ω). A single shock of 30 A was successful in 82·9% (34/41) of episodes and the cumulative success rate for two 30 A shocks was 97·5% (40/41). Only one patient (transthoracic impedance 82 Ω) required a shock of 40 A (311 J delivered) for successful defibrillation.

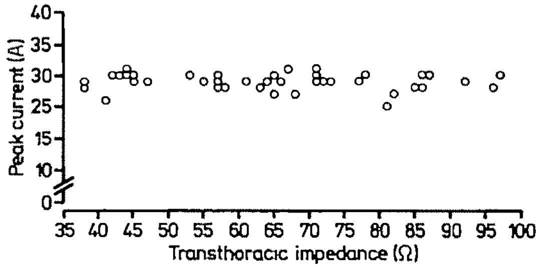


Fig 2 *Graph of peak current versus predicted transthoracic impedance for all 30 A shocks (48 shocks, eight overlapping). A current based defibrillator can deliver a constant current over a wide range of impedances.*

Table *Comparison between the energy and current based protocols*

Data	*Energy protocol*	*Current protocol*	*p*
Episodes	42	41	
Male	33	29	
Female	7	12	
Age (yr, mean)	61 5	63·3	
Predicted mean TTI (Ω)	69 9	65 1	NS
Mean delivered energy for 1st or 2nd successful shocks (J)	200 0	144 8	<0·001
Mean peak current for 1st or 2nd successful shocks (A)	31 9	29 0	<0·05
First shock success (%)	80 9	82 9	NS
First or second shock success (%)	95·2	97 5	NS

TTI, transthoracic impedance.

For successful 30 A shocks the mean energy required by the microprocessor (Ed) was 148·8 (63·8) J (range 63–293 J) and the mean actual delivered energy (Ea) was 144·8 (60·9) J (range 61–282 J). The small difference between the two energy levels is due to component tolerance and operator variability in matching the energy levels on the digital readout.

ENERGY VERSUS CURRENT

A comparison of these groups (table) showed no significant difference in the mean transthoracic impedance. There was also no significant difference in success rates between the groups for the first shock (energy 80·9% versus current 82·9%, $p > 0.05$) and first or second shock (energy 95·2% versus current 97·5%, $p > 0.05$) (table). For first or second successful shocks, however, the mean delivered energy per shock with a current protocol was 144·8 (60·9) J, which was significantly less than the 200 J used for the conventional energy protocol ($p < 0.001$). Also the mean peak current for first or second successful shocks with the current based protocol was 29·0 (1·4) A, significantly less than the mean of 31·9 (5·7) A administered by the energy protocol ($p < 0.05$).

Discussion

DC defibrillation remains a cornerstone of modern cardiology, and since its widespread introduction in the 1960s it has saved thousands of lives. Nevertheless the potentially adverse effects of electrical countershock must not be ignored. It has been shown in animal experiments that microscopic and macroscopic damage are produced in myocardial tissue

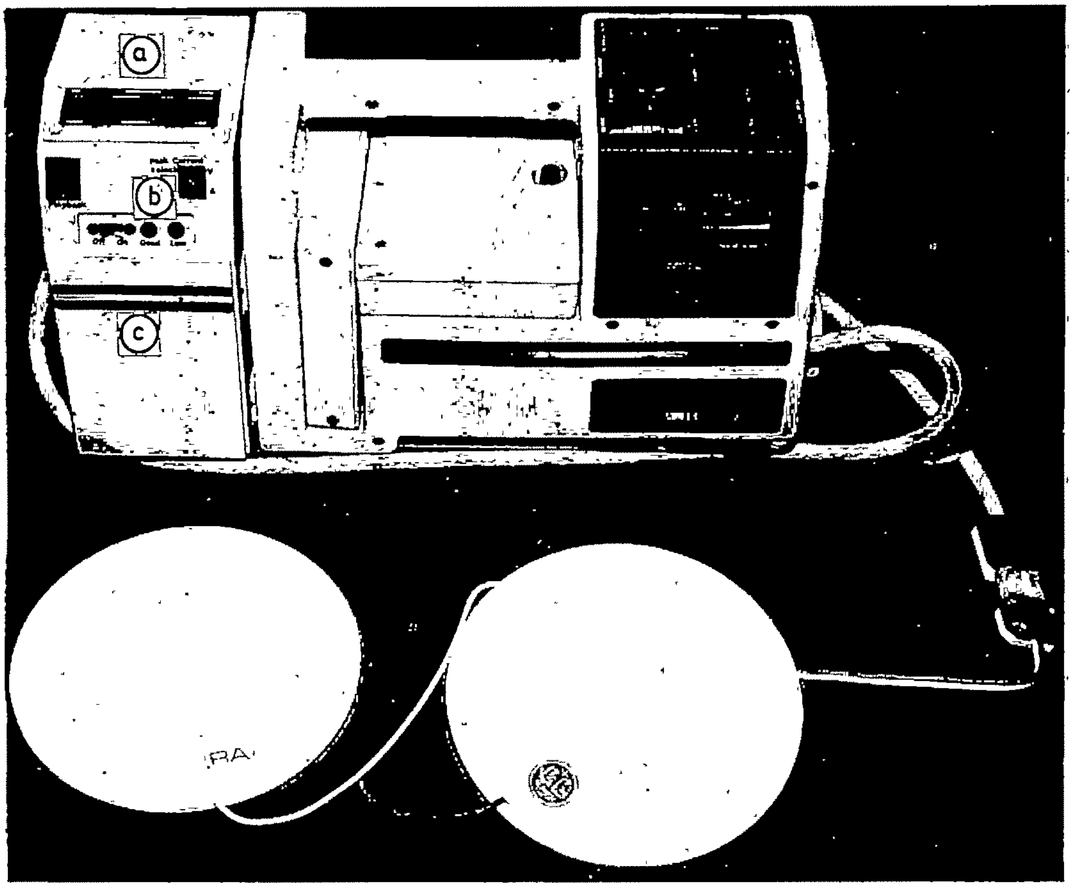


Fig 1 *Microprocessor based current defibrillator. The microprocessor and device for measuring transthoracic impedance is mounted behind a standard lifeguard 6 defibrillator. (a) Digital display; (b) thumbwheel switch; (c) microprocessor.*

thoracic impedance was recorded immediately before defibrillator discharge by a 30 kHz low amplitude (100 μA) current applied via the electrode pads. We have previously shown that this method accurately predicts the actual transthoracic impedance to a defibrillatory shock, both in patients with atrial arrhythmias,[5] and ventricular fibrillation.[6] The peak transthoracic current generated by each discharge was also recorded for each shock.

In the next 41 consecutive patients with 41 episodes of ventricular fibrillation (29 men and 12 women, mean age 63·3 years) we used a microprocessor controlled current based defibrillator (fig 1). In a previous study that we performed in patients with ventricular fibrillation who were defibrillated by an energy protocol the mean peak current for successful defibrillation was 29·2 A.[6] So we decided to use 30 A for the initial shock in this study. If this was unsuccessful we used a second 30 A shock. Subsequent shocks were to be 40 A. The peak current (Is) was selected by means of a thumbwheel switch. The transthoracic impedance was automatically measured by a low amplitude high frequency current method described above. The microprocessor used the current selected, the predicted transthoracic impedance measurement, and pre-programmed defibrillator characteristics to "look-up" the energy required (Ed) to develop the current selected (Is). This energy level was digitally displayed. The defibrillator was then charged by the operator pressing the charge button and matching up the two energies that were displayed side by side on the digital display. This process occurred almost as soon as the charge button was pressed. There was good correlation between the energy required and delivered energy for each patient ($r = 0·98$)

For each shock, the predicted transthoracic impedance, the required energy (Ed), the actual delivered energy (Ea), selected peak current (Is), and actual peak transthoracic current (Ip) were recorded in non-volatile memory and played back where required. The success or failure of each shock was recorded.

We then compared patients treated with the energy protocol with those treated by the current protocol. We analysed continuous variables (transthoracic impedance, peak current, energy) by Student's *t* test, and discrete variables such as defibrillation success by χ^2 and the fourfold table tests. Results are expressed as mean (1 SD).

Results

ENERGY PROTOCOL

The mean predicted transthoracic impedance for this group for first or second shocks was 69·9 (14·0) Ω (range 41·0–100·0 Ω). A single shock of 200 J was successful in 80·9% (34/42) of episodes and the cumulative success rate for two 200 J shocks was 95 2% (40/42). For successful 200 J shocks the mean peak current was 31·9 (5·7) A (range 21·8–46 6 A). This was significantly higher than that for unsuccessful 200 J shocks (28·4 (3·6) A, range 24·8–35·9) ($p < 0.05$).

CURRENT PROTOCOL

For successful shocks where the selected peak current (Is) was 30 A the mean actual peak current (Ip) was 29·0 (1·4) A (range 25·0–31·1 A). Thus the current based defibrillator accurately calculated the required energy to develop the preselected current of 30 A. This system accurately generated a constant current over a wide range of transthoracic impedances (fig 2).

The mean predicted transthoracic impedance of this group for first or second shocks was 65·1 (15 9) Ω (range 38·0–97·0 Ω). A single shock of 30 A was successful in 82·9% (34/41) of episodes and the cumulative success rate for two 30 A shocks was 97·5% (40/41). Only one patient (transthoracic impedance 82 Ω) required a shock of 40 A (311 J delivered) for successful defibrillation.

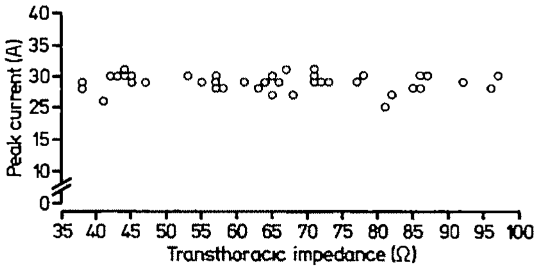


Fig 2 *Graph of peak current versus predicted transthoracic impedance for all 30 A shocks (48 shocks, eight overlapping). A current based defibrillator can deliver a constant current over a wide range of impedances.*

Table *Comparison between the energy and current based protocols*

Data	*Energy protocol*	*Current protocol*	*p*
Episodes	42	41	
Male	33	29	
Female	7	12	
Age (yr, mean)	61 5	63 3	
Predicted mean TTI (Ω)	69 9	65 1	NS
Mean delivered energy for 1st or 2nd successful shocks (J)	200·0	144 8	<0 001
Mean peak current for 1st or 2nd successful shocks (A)	31 9	29 0	<0 05
First shock success (%)	80 9	82 9	NS
First or second shock success (%)	95·2	97 5	NS

TTI, transthoracic impedance.

For successful 30 A shocks the mean energy required by the microprocessor (Ed) was 148·8 (63·8) J (range 63–293 J) and the mean actual delivered energy (Ea) was 144·8 (60·9) J (range 61–282 J). The small difference between the two energy levels is due to component tolerance and operator variability in matching the energy levels on the digital readout.

ENERGY VERSUS CURRENT

A comparison of these groups (table) showed no significant difference in the mean transthoracic impedance. There was also no significant difference in success rates between the groups for the first shock (energy 80·9% versus current 82·9%, $p > 0.05$) and first or second shock (energy 95·2% versus current 97·5%, $p > 0.05$) (table). For first or second successful shocks, however, the mean delivered energy per shock with a current protocol was 144·8 (60·9) J, which was significantly less than the 200 J used for the conventional energy protocol ($p < 0.001$). Also the mean peak current for first or second successful shocks with the current based protocol was 29·0 (1·4) A, significantly less than the mean of 31·9 (5·7) A administered by the energy protocol ($p < 0.05$).

Discussion

DC defibrillation remains a cornerstone of modern cardiology, and since its widespread introduction in the 1960s it has saved thousands of lives. Nevertheless the potentially adverse effects of electrical countershock must not be ignored. It has been shown in animal experiments that microscopic and macroscopic damage are produced in myocardial tissue after countershock.[7] The ultrastructural changes include alterations in membrane permeability with resultant accumulation of intracellular calcium and areas of contraction band formation.[7,8] High shock intensities may produce secondary shock induced membrane depolarisation and hence refibrillation of the ventricle.[9] Also, high energy shocks cause more cardiac damage than low energy shocks.[10]

These effects have been shown only in animal experiments and are subject to the criticism that massive overdoses of energy were generally used. There is only one reported case of macroscopic and microscopic damage induced by DC shock in man.[11] It is not yet known if a single shock of 200 J or 360 J produces myocardial damage in man because of the practical difficulties of detecting such ultrastructural damage. Nevertheless, complete heart block after the correction of ventricular fibrillation in man was more common after 320 J shocks than after 175 J countershocks.[12] The principle that it is best to use the lowest effective energy level remains valid.

It is likely that current rather than energy is more important in successful defibrillation. Successful defibrillation occurs when a significant intramyocardial current causes depolarisation of cells facing the cathode and hyperpolarisation of cells facing the anode.[2] Current density is probably the critical determinant[13] although there is no method of measuring this in man.

During defibrillation the peak transthoracic current generated is determined by the energy selected and by the transthoracic impedance of the patient. It is known that transthoracic impedance varies significantly between patients[14,15] and for this reason use of a fixed energy level will result in a correspondingly variable range of generated transthoracic currents. In this study we showed that a microprocessor based current defibrillator allows energy to be titrated according to the individual patient's transthoracic impedance. This avoids unnecessarily high energy shocks. Patients with a low transthoracic impedance require less energy to generate a peak transthoracic current of 30 A than patients with a high transthoracic impedance.

A current defibrillator that uses a current generator rather than a voltage generator has been developed.[16] This device uses the principle of electromagnetic impulse conservation in an inductor charged with a pre-set current. This unit is cumbersome and it is not portable. Lerman *et al* also suggested a current based system for defibrillation and reported a similar reduction in energy and current for successful shocks delivered to patients undergoing electrophysiological testing.[17] However, this system did not use a microprocessor, and the transthoracic impedance had to be measured in advance of the study with manual calculations before ventricular fibrillation was induced. Obviously such an approach could not be used in emergencies.

We have developed and confirmed the efficacy of a microprocessor controlled current based defibrillator. This system permits the rapid delivery of an accurately calibrated preselected transthoracic current to patients with ventricular fibrillation. Standard defibrillators can be easily modified to become current based systems with the addition of the microprocessor and facilities for measuring transthoracic impedance. This device is as effective as conventional defibrillators but it delivers significantly less energy and current per shock than commercially available energy based machines.

References

1 Zipes DP, Fischer J, King RM, Nicoll A deB, Jolly WW. Termination of ventricular fibrillation in dogs by depolarizing a critical amount of myocardium. *Am J Cardiol* 1975;36: 37–44.

2 Geddes LA, Tacker WA. Ventricular fibrillation and defibrillation. *Australian Physical and Engineering Sciences in Medicine* 1983,6:9–19.

3 Thomas ED, Ewy GA, Dahl CF, Ewy MD Effectiveness of direct current defibrillation. Role of paddle electrode size. *Am Heart J* 1977;93 463–7.

4 Geddes LA, Tacker WA, Schoenlein W, Minton M, Grubbs S, Wilcox P. The prediction of the impedance of the thorax to defibrillating current. *Med Instrum* 1976;10:159–62.

5 Dalzell GWN, Magee H, Anderson J, Adgey AAJ. Predicted and actual impedance in cardioversion [Abstract]. *Circulation* 1986;74(suppl):388.

6 Cunningham SR, Magee H, Anderson J, Adgey AAJ. Patients in ventricular fibrillation—predicted and actual transthoracic impedance and peak current at defibrillation [Abstract]. *PACE* 1987;10:975.

7 Warner ED, Dahl C, Ewy GA. Myocardial injury from transthoracic defibrillator countershock. *Arch Pathol* 1975,99: 55–9.

8 Van Vleet JF, Tacker WA, Geddes LA, Ferrans VJ. Acute cardiac damage in dogs given multiple transthoracic shocks with a trapezoidal wave-form defibrillator. *Am J Vet Res* 1977; 38:617–26.

9 Jones JL, Jones RE. Postshock arrhythmias—a possible cause of unsuccessful defibrillation. *Crit Care Med* 1980;8:167–71.

10 Patton JN, Allen JD, Pantridge JF. The effects of shock energy, propranolol, and verapamil on cardiac damage caused by transthoracic countershock. *Circulation* 1984;69:357–68.

11 Karch SB, Billingham ME. Morphologic effects of defibrillation: a preliminary report. *Crit Care Med* 1984;12:920–1.

12 Weaver WD, Cobb LA, Copass MK, Hallstrom AP. Ventricular defibrillation—a comparative trial using 175 J and 320 J shocks. *N Engl J Med* 1982;307:1101–6.

13 Hoyt R, Grayzel J, Kerber RE. Determinants of intracardiac current in defibrillation. Experimental studies in dogs. *Circulation* 1981;64:818–23.

14 Patton JN, Pantridge JF. Current required for ventricular defibrillation. *Br Med J* 1979;i:513–4.

15 Machin JW. Thoracic impedance of human subjects. *Med Biol Eng Comput* 1978;16:169–78.

16 Monzon JE, Guillen SG. Current defibrillator: new instrument of programmed current for research and clinical use. *IEEE Trans Biomed Eng* 1985;32:928–34.

17 Lerman BB, Haines DE, DiMarco JP, Wesley RC. An improved method for clinical defibrillation: current-based DC countershock [Abstract]. *Circulation* 1986;74(suppl II):389.

Br Heart J 1989;61:506–9

Central haemodynamic changes after a meal

HENNING KELBÆK,* OLE MUNCK,* NIELS J CHRISTENSEN,†
JOHN GODTFREDSEN‡

*From the *Department of Clinical Physiology and Nuclear Medicine, †Department of Internal Medicine and Endocrinology, and ‡Department of Cardiology, Herlev Hospital, University of Copenhagen, Herlev, Denmark*

SUMMARY Eight healthy people (seven men and one woman, aged 19 to 31 years) were studied by radionuclide cardiography when supine before and 30 minutes after a standard meal (6300 kJ). Control investigations were performed on a different day within a week of the standard meal. There was a median increase in cardiac output of 62% that was attributable to a 17% increase in heart rate and a 41% increase in stroke volume. Blood pressure and concentrations of plasma catecholamines did not change. The median end diastolic and end systolic volumes of the left ventricle increased by 41% so that the left ventricular ejection fraction was unchanged. There were no significant changes during the control experiments.

In healthy people a meal caused an appreciable increase in stroke volume and dilatation of the left ventricle. The activity of the sympathetic nervous system, as measured by plasma catecholamines, did not change much, and changes in blood volume alone did not seem to explain the haemodynamic response to the meal.

Cardiovascular changes have been reported during eating and digestion. Experimental studies showed an early rise in cardiac output during eating, which was attributable to an increased heart rate; stroke volume fell.[1 2] Most of the changes reverted to baseline values at the end of eating.[2]

There have been few human studies of the central haemodynamic changes after a meal, and the results of investigations in normal subjects are conflicting.[3 4]

We studied changes in left ventricular volume in healthy young people 30 minutes after a standard meal. We also measured plasma catecholamine concentrations.

Patients and methods

We studied eight healthy people (seven men and one woman; aged 19 to 31 years, median 26 years; median weight 74 kg, range 63 to 94 kg; and height of 1 80 m, range 1·62 to 1·88 m). The study protocol was approved by the local ethics committee.

STUDY PROTOCOL

The volunteers entered the laboratory about three hours after a light breakfast. They were examined after lying down for at least 15 minutes. Baseline investigations were performed before the meal and postprandial investigations 30 minutes after the end of the meal. Volunteers were randomly allocated to have the standard meal or control investigation performed on the first day. Measurements for both studies were performed according to an identical procedure, except for the control study during which the volunteers moved freely for the period corresponding to ingestion of the meal.

STANDARD MEAL

The standard meal (6300 kJ) consisted of 280 g minced beef, 300 g potatoes, 50 g peas, 40 g sliced cucumber, sauce, 150 g stewed apples with 30 g cream, and 400 g low-fat milk. It contained 22% protein, 35% carbohydrate, and 43% fat.

INVESTIGATIONS

Heart rate was monitored electrocardiographically and blood pressure was measured by sphygmomanometry. Blood samples were drawn from a cubital vein for the measurement of plasma adrenaline and noradrenaline by an isotope derivative assay.[5] After in vitro labelling of autologous red blood cells with technetium-99m,[6] cardiac output was measured by first passage radionuclide cardiography[7] with injection of 500 MBq. A cardiac gamma camera equipped with an all purpose

Requests for reprints to Dr Henning Kelbæk, Department of Clinical Physiology and Nuclear Medicine, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark.

Accepted for publication 31 January 1989

parallel hole collimator (Siemens) was positioned in the left anterior oblique projection over the heart to allow optimal separation of the left ventricular chamber. The camera was connected to a dedicated computer system (Scintiview, Siemens) and left ventricular ejection fraction was measured by the multigated equilibrium technique.[8] Left ventricular end diastolic volume was calculated as the stroke volume (cardiac output divided by heart rate) divided by left ventricular ejection fraction, and left ventricular end systolic volume as the end diastolic volume minus stroke volume. Statistical analysis was performed using Pratt's rank test for paired data. A p value $<0\cdot05$ was regarded as significant.

Results

Because the haemodynamic changes in the woman resembled those in the men, we pooled the results (table 1). After the meal cardiac output was increased by a median of 62% because of a 17% increase in heart rate ($p < 0\cdot01$) and a 41% increase in stroke volume ($p < 0\cdot01$) (fig 1). Left ventricular end diastolic and end systolic volumes both increased by 41% ($p < 0\cdot02$), but there was no change in the left ventricular ejection fraction (fig 2). Blood pressure did not change significantly.

Neither plasma adrenaline nor plasma noradrenaline concentrations changed significantly after the meal (table 2).

In the control experiments there were no significant changes in plasma catecholamine concentration or in any haemodynamic variable (tables 1 and 2).

The distribution volume of labelled red blood cells showed an increase from a median of 5·20 l (range 4·14 to 6·14) to 5·61 l (4·46 to 6·95) after the meal ($p < 0\cdot05$). The values in the control study were 5·52 l (4·15 to 6·66) and 5·53 l (3·94 to 6·89) respectively.

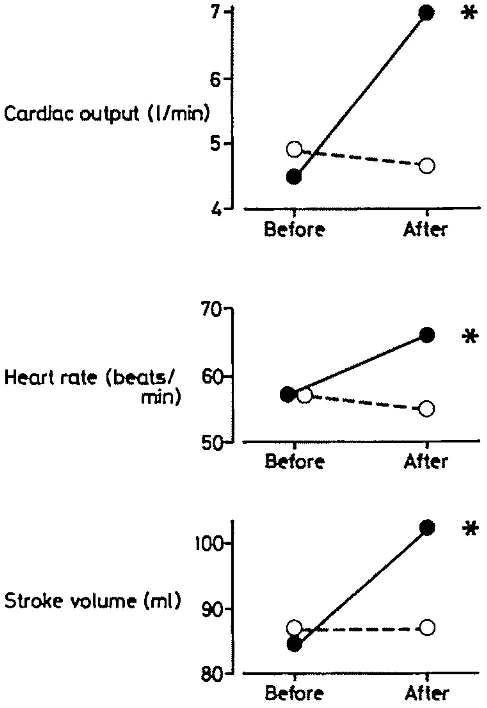


Fig 1 *Haemodynamic variables before and after eating (closed circles). Open circles are values for the control experiments. Median values are shown. *p < 0·01.*

Table 1 *Haemodynamic data before (B) and after (A) ingestion of a standard meal and during a control study in eight healthy people (median (range))*

Data	Standard meal				Control			
	B		*A*		*B*		*A*	
Cardiac output (l/min)	4·40	(3·63–5·69)	6·87**	(6·13–8·16)	4·91	(4·00–5·87)	4·60	(3·87–6·42)
Heart rate (beats/min)	57	(51–65)	66**	(59–76)	57	(49–69)	55	(44–64)
Stroke volume (ml)	85	(58–91)	102**	(86–127)	87	(69–105)	79	(72–117)
Systolic blood pressure (mm Hg)	105	(90–102)	105	(90–130)	100	(95–110)	100	(90–110)
Diastolic blood pressure (mm Hg)	73	(55–85)	60	(55–85)	70	(65–75)	70	(55–75)
Left ventricular ejection fraction (%)	55	(48–68)	58	(50–68)	56	(52–71)	59	(50–67)
Left ventricular end diastolic volume (ml)	138	(112–188)	180*	(141–232)	156	(97–182)	129	(118–208)
Left ventricular end systolic volume (ml)	60	(39–98)	90*	(53–111)	70	(28–87)	56	(39–91)

*p < 0·02, **p < 0·01

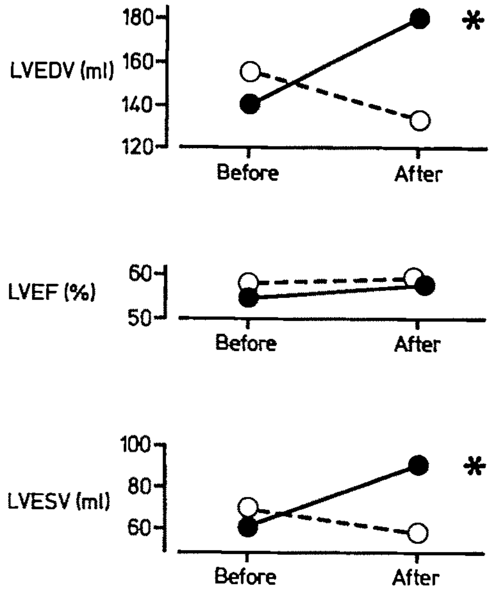


Fig 2 *Left ventricular end diastolic volume (LVEDV), ejection fraction (LVEF), and end systolic volume (LVESV) before and after food (closed circles). Open circles are values of the control experiments. Median values are shown.* *$p < 0·02$.

Discussion

Knowledge of postprandial haemodynamic changes is almost entirely based on experimental studies in animals. In dogs feeding significantly increased cardiac output, heart rate, and arterial blood pressure.[1,2] A rise in blood pressure was also seen in calves[9] and pigs.[10] Nevertheless, there are considerable species differences in the cardiovascular response to feeding.[10] In most of these studies the haemodynamic changes were most prominent during feeding and most of the variables had reverted to baseline values at the end of feeding. So, the buccal phase of digestion may have had a considerable effect.[1,2,10]

Previous studies in healthy people have shown no change in haemodynamic variables[3] or postprandial increases in heart rate, blood pressure, and cardiac output.[4] The discrepancy may be related to differences in size of the meals.

We studied haemodynamic variables in healthy people after a substantial Danish meal (6300 kJ, 1500 kcal). The increase in cardiac output in all individuals after this meal was mostly attributable to an increase in stroke volume. This is at variance with animal studies in which stroke volume fell. Our results indicate that the increase in stroke volume was achieved by a considerable dilatation of the cardiac chambers. These findings are probably unique to primates. The increases in left ventricular end diastolic and end systolic volumes were of similar size, so that the left ventricular ejection fraction was unchanged. In contrast with the results of animal studies,[11] Young *et al* found no significant change in plasma concentrations of catecholamines in healthy young people after ingestion of glucose, fat, or protein.[12] Our results were similar. Thus neither the postprandial increase in heart rate nor the rise in stroke volume can be ascribed to an increased concentration of circulating catecholamines.

When cardiac output is measured by first pass radionuclide cardiography the distribution volume of the injected tracer is measured. This volume may be taken as an indicator of the blood volume and it increased slightly after the meal (by a median of 8%). This rise alone can hardly explain the considerable increase in postprandial cardiac output that we found. In an earlier study the left ventricular ejection fraction increased after a meal in patients with congestive heart failure and moderately depressed values of left ventricular ejection fraction.[13] In another study 10 patients with heart failure showed a postprandial increase in cardiac index.[14] However, spontaneous increases were also found in three out of five patients who were fasting. Such variation emphasises the need for controlled studies.

In our study lack of a change in mean arterial blood pressure and the considerable increase in cardiac output indicate a postprandial reduction in total peripheral resistance of at least 50%. Fronek and Stahlgren reported a 33% increase in flow in the superior mesenteric artery during digestion in dogs.[2] In addition, the increase in intestinal flow was confined to the mucosal and submucosal layers of the duodenum and jejunum 30 to 90 minutes after

Table 2 *Plasma concentration of catecholamines in eight healthy people before (B) and after (A) a standard meal (medians (range))*

	Standard meal				*Control*			
	B		*A*		*B*		*A*	
Adrenaline (ng/ml)	0·02	(0·00–0·04)	0·01	(0·00–0·02)	0·02	(0·00–0·04)	0·02	(0·00–0·03)
Noradrenaline (ng/ml)	0·19	(0·10–0·30)	0·23	(0·13–0·38)	0·16	(0·12–0·25)	0·19	(0·11–0·32)

feeding and to the ileum at 90 minutes, whereas the blood flow to the colon was unchanged during this observation period.[15–17] Thus the cardiovascular response to feeding seems to originate from the digestive organs and tissues. Vasoactive intestinal peptide may be important in these changes.[18] In addition, the influence of the buccal phase of digestion on haemodynamic function remains to be settled.

The physiological implication of our findings is that much of the considerable increase in cardiac output after a meal is attributable to an increase in stroke volume. The increase in stroke volume is probably specific for primates and is achieved by a considerable dilatation of the ventricular chamber(s). Other investigations suggest that the central haemodynamic changes recorded after eating are secondary to changes in intestinal blood flow. Postprandial haemodynamic changes in patients with coronary disease should be studied.

This work was supported by the Danish Medical Research Council, the Danish Heart Foundation, and Novo's Foundation.

References

1 Ehrlich W, Tosheff J, Caldini P, Abbey H, Brady JV. Adaptation of cardiac output, coronary flow and other circulatory functions in dogs to exercise and to eating. *Johns Hopkins Med J* 1972;**130**:216–34.

2 Fronek K, Stahlgren LH. Systemic and regional hemodynamic changes during food intake and digestion in nonanesthetized dogs. *Circ Res* 1968;**23**:687–92.

3 Jones WB, Thomas HD, Reeves TJ. Circulatory and ventilatory responses to postprandial exercise. *Am Heart J* 1965;**69**:668–76.

4 Grollman A. Physiological variations in the cardiac output of man. *Am J Physiol* 1929;**89**:366–70.

5 Christensen NJ, Vestergaard P, Sørensen T, Rafaelsen OJ. Cerebrospinal fluid adrenaline and noradrenaline in depressed patients. *Acta Psychiatr Scand* 1980;**61**:178–82.

6 Kelbæk H, Gjørup T, Fogh J. In vivo stability of in vitro labelled ^{99m}Tc-red blood cells for radionuclide determination of left ventricular ejection fractions and volumes. *Nucl Med Commun* 1986;**7**:541–7.

7 Kelbæk H, Hartling OJ, Skagen K, Munck O, Henriksen O, Godtfredsen J. First pass radionuclide determination of cardiac output: an improved gamma camera method. *J Nucl Med* 1987;**28**:1330–4.

8 Kelbæk H, Gjørup T, Brynjolf I, Christensen NJ, Godtfredsen J, Vestergaard B. Acute effects of alcohol on left ventricular function in healthy subjects at rest and during upright exercise. *Am J Cardiol* 1985;**55**:164–7.

9 Bloom SR, Edwards AV, Hardy RN, Malinkowska K, Silver M. Cardiovascular and endocrine responses to feeding in the young calf. *J Physiol (Lond)* 1975;**253**:135–55.

10 Houpt KA, Baldwin BA, Houpt R, Hills F. Humoral and cardiovascular responses to feeding in pigs. *Am J Physiol* 1983;**244**:R279–84.

11 Landsberg L, Young JB. Fasting, feeding and regulation of the sympathetic nervous system. *N Engl J Med* 1978;**298**:1295–301.

12 Young JB, Rowe JW, Pallotta JA, Sparrow D, Landsberg L. Enhanced plasma norepinephrine response to upright posture and oral glucose administration in elderly human subjects. *Metabolism* 1980;**29**:532–9.

13 Brown JM, White CJ, Sobol SM, Lull RJ. Increased left ventricular ejection fraction after a meal: potential source of error in performance of radionuclide angiography. *Am J Cardiol* 1983;**51**:1709–11.

14 Cornyn JW, Massie BM, Unverferth DV, Leier CV. Hemodynamic changes after meals and placebo treatment in chronic congestive heart failure. *Am J Cardiol* 1986;**57**:238–41.

15 Chou CC, Hsieh CP, Yu YM, *et al.* Localization of mesenteric hyperemia during digestion in dogs. *Am J Physiol* 1976;**230**:583–9.

16 Gallavan RH, Chou CC, Kvietys P, Sit SP. Regional blood flow during digestion in the conscious dog. *Am J Physiol* 1980;**238**:H220–5.

17 Vatner SF, Patrick TA, Higgins CB, Franklin D. Regional circulatory adjustments to eating and digestion in the conscious unrestrained primate. *J Appl Physiol* 1974;**36**:524–9.

18 Frase LL, Gaffney FA, Lane LD, *et al.* Cardiovascular effects of vasoactive intestinal peptide in healthy subjects. *Am J Cardiol* 1987;**60**:1356–61.

Br Heart J 1989;61:510–3

The QT interval in atrial fibrillation

G R PAI, J M RAWLES

From the Department of Medicine and Therapeutics, University of Aberdeen

SUMMARY The electrocardiogram was recorded for 100 seconds in 50 patients with atrial fibrillation to determine the relations between QT intervals and both the mean and instantaneous ventricular rates. The mean ventricular rate was 94 beats per minute with a mean QT interval of 357 ms. The mean QTc, corrected beat by beat with Bazett's formula, was 444 ms—longer than reported for sinus rhythm. Between subjects, the mean QT interval was linearly related to the mean RR interval, with a slope of +21%. Within all 50 recordings there was a statistically significant correlation between QT intervals and immediately preceding RR intervals, with an average slope of +7%. This within subject QT/RR interval slope was greater at faster mean ventricular rates. In atrial fibrillation, as in sinus rhythm, the QT interval is a function of both the mean ventricular rate and the instantaneous ventricular rate, with the mean ventricular rate predominating; a simple correction of QT intervals for heart rate is therefore inadequate. Comparison of uncorrected QT intervals with those of earlier published series of people in sinus rhythm, however, suggested that atrial fibrillation is associated with prolongation of the mean QT interval.

The duration of the QT interval of the electrocardiogram is a function of the heart rate; it is positively correlated with preceding RR intervals. Before a QT interval can be assessed in sinus rhythm, its duration must be adjusted for the mean RR interval or heart rate. For this purpose various formulas have been used that imply a linear relation between the QT interval and the RR interval (Schlamowitz,[1] Simonson *et al*[2]), or its square root (Bazett[3]), cube root (Fridericia[4]), or logarithm (Ashman[5]).

It has recently been shown, however, that the duration of the QT interval depends not only on the prevailing heart rate but also on the instantaneous interval between beats.[6] When the paced heart rate was suddenly increased and then maintained, there was an immediate shortening of the QT interval followed by a further more gradual shortening over several minutes. These observations imply that a simple correction of QT interval for heart rate is inadequate.

Atrial fibrillation is characterised by considerable beat to beat changes of heart rate, with a wide range of mean heart rates in different subjects. It therefore provides an opportunity to examine the QT interval as a function of both the instantaneous and the mean heart rate. We examined the relations between QT and RR intervals within and between 50 patients with atrial fibrillation.

Patients and methods

PATIENTS

We studied 50 patients (19 men and 31 women; aged 31–87 (mean 70)) with established atrial fibrillation. The causes of atrial fibrillation were: idiopathic, 26; ischaemic heart disease, nine; valvar heart disease, six; pulmonary disease, six; and thyrotoxicosis, three. Thirty one patients were taking digoxin; none was taking other drugs known to affect the QT interval.

ELECTROCARDIOGRAM RECORDINGS AND MEASUREMENT

Patients lay down for 15 minutes before an average of 151 beats were recorded by a standard lead I at a paper speed of 25 mm/second. The QT and RR intervals were measured with a digitising pad and microcomputer with a resolution of 0·1 mm, equivalent to 4 ms; the results were stored on disc. The average (SD) difference between replicated measurements of 213 RR intervals was 0·20 (10·8) ms.

STATISTICAL ANALYSIS

We used Bazett's equation[3] to correct QT intervals

Requests for reprints to Dr J M Rawles, Department of Medicine and Therapeutics, University of Aberdeen, Foresterhill, Aberdeen AB9 2ZD.

Accepted for publication 14 February 1989

for heart rate: $QTc = QT/(RR)^{1/2}$, where RR is in seconds. It was used in two ways: either each QT interval was corrected by the preceding RR interval and the mean corrected QT interval of all beats was calculated, or we corrected the mean QT interval for each patient using the mean RR interval.

Linear and multiple regression was carried out to study the relations between QT and RR intervals, and paired and unpaired t tests were used as appropriate to compare means.

Results

MEAN RR, QT, AND QTC INTERVALS

The table shows the averages of mean heart rate, RR, QT, and QTc intervals. None of these measurements was significantly different in men or women, in those taking or not taking digoxin, or in those aged over 69 or under 70.

Correction of QT intervals beat by beat gave significantly higher values than the mean RR intervals ($p < 0{\cdot}001$). Of 50 patients, 28 had a mean QTc >440 ms corrected beat by beat compared with 22 when corrected by RR interval means. There was no relation between a prolonged QTc and diagnosis.

Figure 1 shows the distribution of mean RR and QT intervals in our 50 patients with atrial fibrillation in relation to the normal range in 6000 cases in sinus rhythm (data of Lepeshkin, redrawn from Ahnve[7]). Most cases fall in the upper half of the normal distribution but in eight cases the mean QT interval is excessive for the mean RR interval.

RELATION BETWEEN MEAN QT AND MEAN RR INTERVALS BETWEEN PATIENTS

The mean QT and RR intervals in 50 subjects were positively correlated ($r = 0{\cdot}77$, $p < 0{\cdot}001$), and the regression equation was $QT = 213 + 0{\cdot}21\,(RR)$, where both the QT and RR intervals are expressed in ms (fig 1). The regression lines for the data of Schlamowitz,[1] Simonson *et al*,[2] and Ahnve[7] are shown for comparison.

The slope of the regression line for the relation between QT and RR intervals in atrial fibrillation was not significantly different in men or women, in those taking or not taking digoxin, or in those aged 69 or under 70. Inspection of the plot shows no obvious non-linearity, but the correlation coefficient was slightly increased, from 0·77 to 0·78, when $RR^{1/2}$ was used in place of mean RR.

Table *Averages (SD) of mean heart rate, RR, QT, and QTc intervals corrected beat by beat or by mean RR in 50 patients with atrial fibrillation*

Variables (beats/min)	*Mean (SD)*
Heart rate	94·0 (26·5)
RR intervals (ms)	683·6 (173·1)
QT intervals (ms)	357·6 (47·7)
QTc (beat) intervals (ms)	443·7 (38·6)
QTc (mean) intervals (ms)	437·4 (37·7)

RELATION BETWEEN QT AND RR INTERVALS WITHIN PATIENTS

In every case, QT intervals were positively correlated with immediately preceding RR intervals ($p < 0{\cdot}001$ in 41; $p < 0{\cdot}01$ in six; $p < 0{\cdot}05$ in three); the average of the correlation coefficients was 0·44. Only in eight cases were QT intervals significantly correlated with pre-preceding RR intervals as well (six negative, two positive).

In fig 2 the slopes of the individual QT/RR interval relations are plotted against mean RR intervals. The average slope was 7%, and the shorter the mean RR interval, the higher the heart rate, the greater the slope, and the greater the influence of the preceding RR interval on the QT interval. However, the average slope within individuals was only a third of that between individuals, and every within individual slope was less than that between individuals (fig 3).

Figure 4 shows a plot of QT and RR intervals in a 76 year old woman with a mean ventricular rate of 76. In this case the relation is better described as quadratic than linear. In 31 cases a quadratic equation gave a slightly better fit, and the average multiple correlation coefficient for the quadratic equation was 0·45 compared with 0·44 for linear regression.

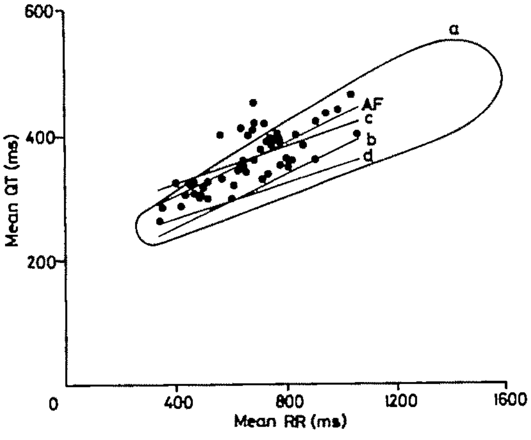


Fig 1 *Scatter plot and regression line of mean QT and RR intervals in 50 patients with atrial fibrillation (AF) in relation to (a) the range of values in 6000 healthy subjects (Lepeshkin[8]), (b) the regression line from 495 healthy subjects (Schlamowitz[1]), (c) the regression line from 960 healthy subjects (Simonson et al[2]), and (d) the regression line from 152 patients with ischaemic heart disease on digitalis (Ahnve[7]).*

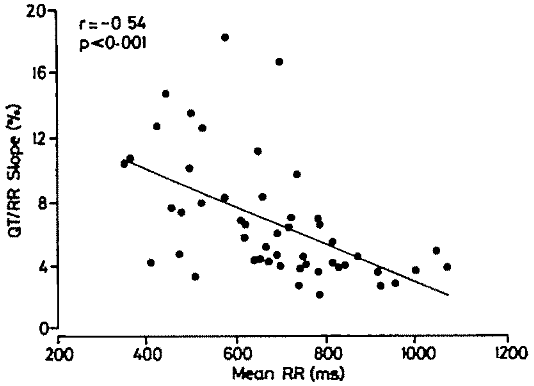


Fig 2 *Scatter plot and regression line of the within subject QT/RR interval slope and the mean RR interval in 50 patients with atrial fibrillation.*

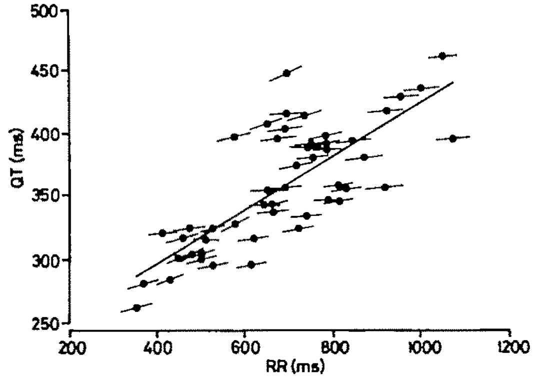


Fig 3 *Regression lines for the between subject and within subject QT/RR interval relations in 50 patients with atrial fibrillation.*

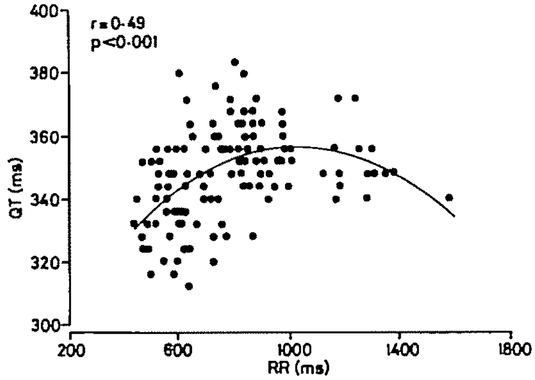


Fig 4 *QT and RR intervals and the best fit quadratic regression line in a 76 year old woman with atrial fibrillation.*

Discussion

The QT interval of the surface electrocardiogram corresponds to electrical systole, during which ventricular muscle is depolarised, as may be shown by unipolar electrodes placed within the heart. If there is a regular ventricular rate and an extra stimulus is applied immediately after depolarisation there is no response, and the ventricle is said to be refractory. If the stimulus is applied later then depolarisation occurs, but its duration depends on the interval between the previous beat and the stimulus. The curve depicting the relation between the delay in the stimulus and the duration of depolarisation is called the restitution curve. The shape and position of the restitution curve are affected by the basic ventricular rate, being depressed at higher heart rates. A change of ventricular rate produces an immediate change in the duration of depolarisation and the QT interval followed by a more gradual change over the next few minutes.[6]

In atrial fibrillation each beat may be considered as a depolarising stimulus, occurring a variable time after the preceding beat. The duration of the subsequent QT interval will vary according to the restitution curve at that particular mean ventricular rate. The within subject QT/RR interval relation corresponds to the restitution curve except that, in contrast with the experimental situation and with sinus rhythm, the rhythm of ventricular contraction is irregular. In atrial fibrillation, therefore, both instantaneous and mean ventricular rates would be expected to determine the duration of the QT interval: this is what we showed. The influence of the mean ventricular rate exceeded that of the instantaneous ventricular rate, the slope of the QT/RR interval relation between subjects being 21%, compared with an average of 7% within subjects. An increasing mean ventricular rate altered both the position and the slope of the within subject QT/RR interval relation; it depressed the position and increased the slope.

IS THE QT INTERVAL IN ATRIAL FIBRILLATION DIFFERENT FROM THAT IN SINUS RHYTHM?

The occurrence of atrial fibrillation implies some underlying cardiac abnormality which was overt in many of our cases. It is therefore difficult to be sure whether any differences from normal of QT intervals are due to the arrhythmia, or the pathological process that caused it. Ischaemia and inflammation are important causes of QT prolongation,[8] but no patient was known to have any cardiac inflammatory process, and none of the patients with ischaemic heart disease had ischaemia at rest or had recently had a myocardial infarction. A second difficulty is that of correction for heart rate.

In atrial fibrillation the relation between heart rate and QT interval is complex and not readily encompassed by a simple equation such as those proposed for sinus rhythm. It is therefore inappropriate to correct QT intervals with a formula such as Bazett's. When we used Bazett's formula on a beat to beat basis 28 of 50 patients had a mean QTc above the upper limit of normal of 440 ms; whereas a scatter plot of mean uncorrected QT and RR intervals showed only eight definitely abnormal results compared with Lepeschkin's results in 6000 healthy subjects with sinus rhythm[8] (fig 1). Schlamowitz carried out linear regression of QT against RR intervals in 495 people in sinus rhythm.[1] The correlation coefficient of 0·78 was similar to the between patient correlation in our study of patients with atrial fibrillation. His regression line seems to fit the data of Lepeshkin very well, but is parallel to and below our regression line for patients with atrial fibrillation. The regression line for Simonson *et al*'s data from 960 healthy people has a lower slope and crosses our own at its midpoint.[2] Ahnve described the regression line from 152 patients with ischaemic heart disease on digitalis, and that line too lay below our own.[7]

We tentatively conclude that in atrial fibrillation uncorrected QT intervals are generally longer than they are at the same ventricular rate in sinus rhythm, but only a few mean QT intervals fall outside the wide range encountered in the largest published series. Comparison with data from patients with ischaemic heart disease suggests that the prolongation of QT intervals in atrial fibrillation may result from the arrhythmia rather than any underlying abnormality.

G R Pai was supported by a research grant from the Merrell Dow Research Institute. A research grant from Grampian Health Board is gratefully acknowledged.

References

1 Schlamowitz I. An analysis of the time relationships within the cardiac cycle in electrocardiograms of normal men. I. The duration of the Q–T interval and its relationship to the cycle length (R-R interval). *Am Heart J* 1946;31:329–42.

2 Simonson E, Cady LD, Woodbury M. The normal Q-T interval. *Am Heart J* 1962;63:747–53.

3 Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1920;7:353–70.

4 Fridericia LS. Die Systolendauer im Elektrokardiogramm bei normalen Menshen und bei Herzkranken. *Acta Med Scand* 1920;53:469–86.

5 Ashman R. The normal duration of the Q-T interval. *Am Heart J* 1942;23:522–34.

6 Seed WA, Noble MIM, Oldershaw P, *et al.* Relation of human cardiac action potential duration to the interval between beats: implications for the validity of rate corrected QT interval (QTc). *Br Heart J* 1987;57:32–7.

7 Ahnve S. Correction of the QT interval for heart rate: review of different formulas and the use of Bazett's formula in myocardial infarction. *Am Heart J* 1985;109:568–74.

8 Lepeschkin E. *Modern electrocardiography,* vol 1. Baltimore: The Williams and Wilkins Co, 1951: 180–8.

Br Heart J 1989;**61**:514–20

Right ventricular infarction: diagnostic accuracy of electrocardiographic right chest leads V3R to V7R investigated prospectively in 43 consecutive fatal cases from a coronary care unit

HENNING RUD ANDERSEN, ERLING FALK,* DORTHE NIELSEN

*From the Departments of Cardiology, Skejby Sygehus and Aalborg Sygehus, and *Institute of Forensic Medicine, Odense University, Denmark*

SUMMARY The accuracy of ST elevation $\geqslant 1$ mm in right chest leads V3R to V7R in the diagnosis of right ventricular infarction was investigated in a clinical and necropsy study of 43 consecutive patients who died in a coronary care unit. Thirty six patients had left ventricular myocardial infarction and in 27 the right ventricle was also affected. Seven patients had normal hearts. The specificity and positive predictive value of ST elevation in V3R were 81% and 77%, respectively. These increased to 100% when combined with ST elevation in one or more leads V4R–V7R. The diagnostic accuracy was poor for anterior infarcts (sensitivity $\leqslant 27\%$), but high for inferior/posterior infarcts (sensitivity $\geqslant 64\%$) in which the specificity and positive predictive value reached 100% in V6R and V7R.

Inferior/posterior infarction affecting the right ventricle can be diagnosed reliably by examination of electrocardiograms from right chest leads V6R and V7R.

The first pathological report on right ventricular infarction was published in 1930 by Sanders.[1] In 1974, Erhardt suggested that ST segment elevation in right chest lead CR4R was a good indicator of extensive right ventricular infarction.[2] Since then, many studies have evaluated the diagnostic value of various right chest leads in right ventricular infarction. Most electrocardiographic studies have examined two leads only (V3R and V4R) and conflicting results have been reported.[3-8] A few studies have focused on more lateral right chest leads[9-13] and in two of these studies the lateral right chest leads V5R and V6R were claimed to be most accurate.[9 11] Right ventricular infarct size and location, however, were not confirmed at necropsy in these two studies.

The aim of this prospective study was to evaluate the diagnostic value of right chest leads V3R to V7R in right ventricular infarction in consecutive patients from a coronary care unit whose hearts were examined at necropsy.

Patients and methods

STUDY PATIENTS

From November 1984 to January 1986, consecutive patients with clinically suspected ischaemic heart disease were prospectively included in a study of right ventricular infarction. The hearts of patients who died in hospital were examined for evidence of right ventricular infarction.[14]

Patients who died were included in the present study if (*a*) there was no previous myocardial infarction (recognised clinically or electrocardiographically); (*b*) an electrocardiogram was recorded within 12 hours of the onset of symptoms, and (*c*) the electrocardiogram did not show bundle branch block. Forty three patients fulfilled these criteria (15 women and 28 men; median age 67 years, range 44–84 years). Thirty six patients died from acute myocardial infarction and seven from non-cardiac disease.

ANATOMICAL INVESTIGATION

The necropsy technique has been described in detail elsewhere.[14] In brief, we performed postmortem coronary arteriography followed by cross sectioning

Requests for reprints to Dr Henning Rud Andersen, Department of Cardiology, Skejby Sygehus, Aarhus University Hospital, DK-8200 Aarhus N, Denmark.

Accepted for publication 9 February 1989

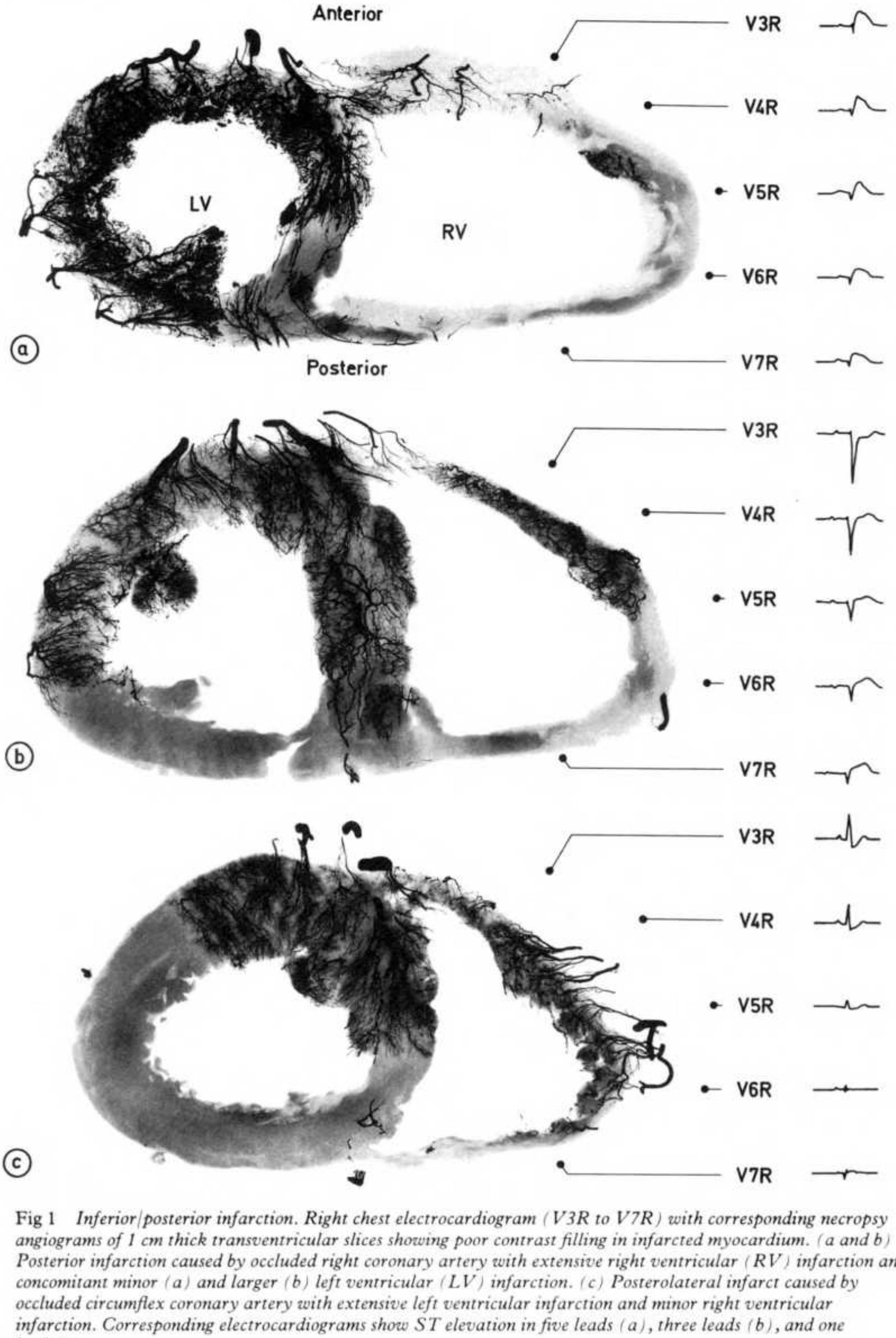


Fig 1 *Inferior/posterior infarction. Right chest electrocardiogram (V3R to V7R) with corresponding necropsy angiograms of 1 cm thick transventricular slices showing poor contrast filling in infarcted myocardium. (a and b) Posterior infarction caused by occluded right coronary artery with extensive right ventricular (RV) infarction and concomitant minor (a) and larger (b) left ventricular (LV) infarction. (c) Posterolateral infarct caused by occluded circumflex coronary artery with extensive left ventricular infarction and minor right ventricular infarction. Corresponding electrocardiograms show ST elevation in five leads (a), three leads (b), and one lead (c).*

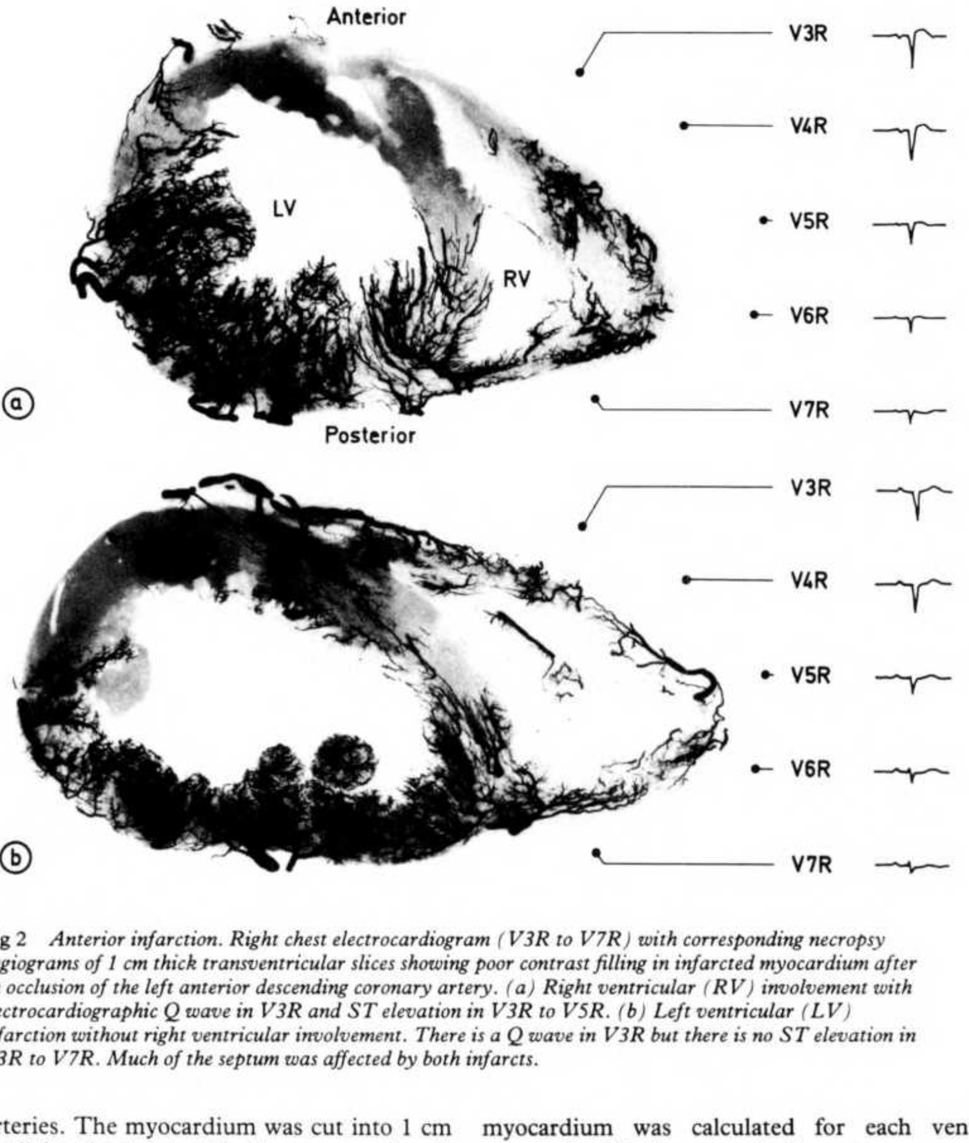


Fig 2 *Anterior infarction. Right chest electrocardiogram (V3R to V7R) with corresponding necropsy angiograms of 1 cm thick transventricular slices showing poor contrast filling in infarcted myocardium after an occlusion of the left anterior descending coronary artery. (a) Right ventricular (RV) involvement with electrocardiographic Q wave in V3R and ST elevation in V3R to V5R. (b) Left ventricular (LV) infarction without right ventricular involvement. There is a Q wave in V3R but there is no ST elevation in V3R to V7R. Much of the septum was affected by both infarcts.*

of the arteries. The myocardium was cut into 1 cm slices parallel to the atrioventricular groove and each slice was photographed, *x* rayed (figs 1 and 2), and photographed again after incubation in a nitroblue tetrazolium solution to improve the definition of the infarct. New and old infarcts were identified as regional myocardial necrosis or regional myocardial scar tissue (fibrosis) distal to an appropriate coronary artery lesion,[15] and were classified as anterior, lateral, or posterior.[16] The right septal wall was taken on the boundary between the right and the left ventricle.[14] Computer assisted planimetry was performed on colour prints of each myocardial slice, and the total weight of ventricular myocardium and infarcted myocardium was calculated for each ventricle separately. The interventricular septum was regarded as part of the left ventricle.

ELECTROCARDIOGRAPHIC RECORDING AND MEASUREMENTS

A 12 lead electrocardiogram (I, II, III, aVR, aVL, aVF, V1 to V6) and five right chest leads (V3R to V7R) were recorded. The electrocardiograph was a three channel ink-jet Siemens Elema Mingograph 34 galvanometer recorder (Siemens Elema AB). The paper speed was 25 mm/s and manual calibration (1 mV = 10 mm) was adjusted before the recordings. Measurements were obtained according to the

Minnesota code criteria.[17] The ST segment was measured 40 ms after the last nadir in the QRS complex in leads II, III, aVF, and V3R–V7R. Three consecutive QRS complexes were evaluated with the PQ level as the isoelectrical line. Elevation of the ST segment was estimated to the nearest ¼ mm by careful visual inspection. The mean value for three consecutive ST segments was calculated. Abnormal ST elevation was defined as a deviation >0·6 mm in V3R, >0·5 mm in V4R to V6R, and >0·4 mm in V7R.[18] Because it is difficult for the human eye to detect ST elevation of 0·4 to 0·6 mm with precision, we also evaluated ST elevation ⩾1 mm, which has been reported to be a useful clinical marker of right ventricular infarction.[3 5–7 13]

The electrocardiographic site of the infarct was classified as anterior or posterior if characteristic changes were seen in at least two leads in the 12 lead electrocardiogram.[19] Changes in V1–V3 (anteroseptal), V1–V6 (extensive anterior), or V4–V6, I, aVL, and possibly II (anterolateral) were all classified as anterior. Changes in II, III, aVF (inferior), inverse changes in V1–V3 (true posterior), and II, III, aVF, V5, V6, and sometimes also I and aVL (inferolateral) were classified as posterior. If no such changes were seen the infarct location was unclassified.

INFARCT GROUPS

Patients were grouped according to the presence or absence of anatomical right ventricular infarction. Furthermore, infarct locations determined by anatomical and electrocardiographic criteria were considered separately, particularly anterior and posterior locations.

STATISTICAL ANALYSIS

Pathological, anatomical, and electrocardiographic data are presented as median and range. We used the Mann-Whitney U test to compare median values in two groups and the Kruskal-Wallis test to compare median values in more than two groups. We used Fisher's exact test to compare frequencies. Coefficients of correlation (Spearman rho) were calculated. The level of significance was $p < 0·05$, and two sided tests were performed. The diagnostic accuracy of ST elevation and Q wave was calculated.[20]

Table 1 *Anatomical and electrocardiographic (ECG) location of 36 acute myocardial infarcts in 36 patients*

ECG infarct location	*Anatomical infarct location* *Anterior 18 (15)*	*Posterior 12 (11)*	*Lateral 6 (1)*
Anterior 17	16 (14)	1 (1)	0
Posterior 16	1 (0)	11 (10)	4 (1)
Unspecified 3	1 (1)	0	2 (0)

Figures in parentheses are infarcts with anatomical right ventricular involvement.

Results

ANATOMICAL FINDINGS

Seven patients died from non-cardiac disease and had normal hearts without appreciable disease of the coronary arteries, valves, or myocardium. Three of these patients died from pneumonia; arrhythmia, pulmonary embolism, perforation of a peptic ulcer, and unspecified haematological disease was the cause of death in the remaining four patients. Thirty six patients died from acute myocardial infarction, and necropsy showed old infarcts in 17 although they had had no clinical or electrocardiographic evidence of previous infarction. Thirteen patients died from myocardial rupture, 12 from cardiogenic shock, seven from arrhythmia, two from ischaemic brain damage after cardiac arrest, one from acute bronchial asthma, and one from heart failure (within days).

Table 1 lists the anatomical site and corresponding electrocardiographic location of the 36 acute myocardial infarcts and whether or not the right ventricle was affected. In 27 cases (75% of infarcts) it was—about half were anterior infarctions and half were posterior infarctions, and only one was a left lateral infarction.

Table 2 shows the amount of infarcted myocardium in the left and right ventricle in anterior,

Table 2 *Size, site, and distribution of acute myocardial infarction in 36 patients*

	Anatomical infarct location *Anterior n = 18*	*Posterior n = 12*	*Lateral n = 6*	*p value*
Total infarct size (gm)	40 (4–91)	40 (11–99)	38 (12–113)	NS*
Left ventricular infarct size (gm)	39 (4–84)	19 (3–72)	38 (8–103)	<0·05*
Right ventricular infarct size (gm)	2 (0 1–7)	15 (5–32)	(n = 1)	<0 05**
Percentage of left ventricle infarcted	28 (4–84)	16 (2–33)	29 (6–51)	<0·05*
Percentage of right ventricle infarcted	5 (1–21)	53 (25–72)	—	<0 05**
Percentage of septum infarcted	48 (8–87)	11 (0–32)	—	<0·05**

*Posterior infarction compared with anterior or lateral infarction (Kruskal-Wallis test)
**Posterior infarction compared with anterior infarction but not with lateral infarction (Mann-Whitney test).
Septum included in the left ventricle.

Table 3 *Diagnostic accuracy (%) of right chest leads in 43 patients with or without right ventricular infarction by necropsy*

	Sensitivity	*Specificity*	*Positive predictive value*	*Negative predictive value*	*Efficiency*
ST elevation ≥ 1 mm in leads:					
V3R	37 (44)	81 (81)	77 (80)	43 (46)	53 (58)
V4R	33 (41)	86 (76)	82 (85)	44 (47)	53 (58)
V5R	26 (44)	94 (81)	88 (80)	43 (46)	51 (58)
V6R	33 (41)	100 (88)	100 (85)	47 (47)	58 (58)
V7R	41 (44)	100 (81)	100 (80)	50 (50)	63 (58)
Q wave in V3R	37	87	83	45	56

Numbers in parentheses are percentages with abnormal ST elevation (V3R > 0·6 mm, V4R to V6R > 0 5 mm, V7R > 0·4 mm[18]).

posterior, and lateral infarcts. Total infarct size was not significantly different in these sites, but there was quite a different pattern of infarct distribution between the ventricles in anterior and posterior infarcts. The right ventricular infarct component was much larger in posterior infarction than in anterior infarction. Lateral infarcts could not be considered further because there was only one with right ventricular involvement.

ELECTROCARDIOGRAPHIC FINDINGS

The 12 lead electrocardiogram and the right chest leads were normal in the seven patients without heart disease. Tables 3 and 4 show the sensitivity, specificity, positive and negative predictive value, and efficiency for ST elevation and Q wave.

ST ELEVATION AND Q WAVE

The diagnostic accuracy of ST elevation of ≥1 mm in right chest leads was higher for lateral than for medial leads and reached 100% specificity and positive predictive value in leads V6R and V7R (table 3). The diagnostic accuracy of ST elevation varied with different infarct sites. The sensitivity was <28% in anatomical anterior infarction, but >63% in posterior infarcts. The same differences were found for electrocardiographic anterior and posterior infarction. The sensitivity was >63% in electrocardiographic posterior infarction where specificity and positive predictive value reached 100% in V5R, V6R, and V7R (table 4). The positive predictive value of ST elevation in V6R and V7R fell from 100% to 80–85% when abnormal ST elevation rather than ≥1 mm was used as the discriminator (table 3).

The positive predictive value of a Q wave in lead V3R was 83% for all infarcts (table 3). The positive predictive value was 86% for anatomical anterior infarcts, but 100% for anatomical posterior infarcts. Use of a combination of Q wave in V3R and ST elevation in leads V5R–V7R did not improve the diagnostic accuracy.

NUMBER OF LEADS WITH ST ELEVATION

There was a positive correlation between the number (1–5) of right chest leads with ST elevation ≥1 mm and the size (g) of right ventricular infarction (rho = 0·41, $p < 0·05$). An inverse and non-significant correlation was found between the number of leads with ST elevation ≥1 mm and the size of left ventricular infarction (rho = −0·23, NS). ST elevation ≥1 mm in all five right chest leads (V3R–V7R) was always associated with extensive right ventricular infarction (median 62%, range 36–72% of the right ventricle infarcted) with concomitant small left ventricular infarction (median 14%, range 7–16%) of the left ventricle infarcted (fig 1a). ST elevation of ≥1 mm in both of the two medial leads (V3R and V4R) was found in 10 patients and was associated with right ventricular infarction in eight. The other two patients had left (anterior) ventricular infarction without right ventricular involvement (fig 2b). ST

Table 4 *Diagnostic accuracy (%) of right chest leads in 16 patients with electrocardiographic posterior infarction. Infarct location was examined at necropsy*

	Sensitivity	*Specificity*	*Positive predictive value*	*Negative predictive value*	*Efficiency*
ST elevation ≥ 1 mm in leads:					
V3R	37 (44)	81 (81)	77 (80)	43 (46)	53 (58)
V4R	33 (41)	86 (76)	82 (85)	44 (47)	53 (58)
V5R	26 (44)	94 (81)	88 (80)	43 (46)	51 (58)
V6R	33 (41)	100 (88)	100 (85)	47 (47)	58 (58)
V7R	41 (44)	100 (81)	100 (80)	50 (50)	63 (58)
Q wave in V3R	37	87	83	45	56

Numbers in parentheses are percentages with abnormal ST elevation (V3R > 0·6 mm, V4R to V6R > 0 5 mm, V7R > 0 4 mm[18]).

elevation of ≥1 mm in the three lateral leads (V5R–V7R) was always associated with posterior infarction with right ventricular involvement. Furthermore, ST elevation of ≥1 mm in all five right chest leads was always associated with occlusion of the right coronary artery proximal to the marginal (acute) branch.

Discussion

ANATOMICAL FINDINGS

Anterior right ventricular infarcts were always small and mainly located in the apical third of the heart far from the right chest leads. Posterior right ventricular infarcts were often large and located near the atrioventricular groove, closer to the right chest leads. Therefore we expected that electrocardiographic infarct signals from the right ventricle would be stronger and easier to detect in posterior infarction than in anterior infarction.

DIAGNOSTIC ACCURACY OF ST ELEVATION

ST elevation of ≥0·5 mm in right chest leads has been reported to be diagnostic for right ventricular infarction.[5-7] Recently, normal values for ST elevation were published; these indicated that ST elevation of 0·4–0·6 mm in various right chest leads should be accepted as normal.[18] Therefore, to secure interpretation of a valid abnormal signal in practice, we recommend ST ≥1 mm as the discriminatory level. Using this criterion, we found that positive predictive value and specificity were 100% in leads V6R and V7R. This is even higher than the results obtained by Funk who evaluated ST elevation of ≥1 mm in V6R.[9]

DIAGNOSTIC ACCURACY OF Q WAVE

Loss of the rightwardly directed electrical vector generated from activation of the right ventricle and the septum[19] may be responsible for the abnormal Q wave in V3R. So a Q wave in V3R may reflect septal necrosis as well as right ventricular necrosis. Therefore in anterior infarction extensive septal necrosis (loss of a rightwardly directed vector) with small right ventricular involvement (fig 2a) may be responsible for the smaller positive predictive value for this infarct site. In posterior infarction (fig 1), a Q wave in V3R was more likely to reflect right ventricular necrosis.

NUMBER OF LEADS

Erhardt *et al* used only one right chest lead (CR4R).[2 7] Since then, most studies were limited to two leads (V3R and V4R) and very few studies investigated multiple right chest leads.[9-13] Braat *et al* found the best diagnostic result with lead V4R[10] whereas Croft *et al* found that a combination of V4R, V5R, and V6R was the most reliable.[11] Funk, however, found the highest diagnostic sensitivity and specificity for V6R; diagnostic efficiency was not improved by combining V6R with changes in V4R and V5R.[9] The present study confirms the observations of Funk[9] and Carson[13] that diagnostic accuracy is greatest for lateral right chest leads, and is not significantly improved by combining these leads with the more medial leads.

The number of right chest leads showing ST elevation ≥1 mm decreased as the size of left ventricular infarction increased. Patients with extensive right ventricular infarction and large left ventricular infarction may be without ST elevation in V3R and V4R while leads V5R to V7R show ST elevation ≥1 mm (fig 1b). This may be caused by the abolition of ST elevation in leads V3R and V4R by the large left ventricular infarction. Furthermore, large infarcts of the left ventricular lateral wall with minor right ventricular involvement may cause ST depression in most of the right chest leads (fig 1c).

CLINICAL IMPLICATIONS

The electrocardiographic diagnosis of acute myocardial infarction is normally based upon changes in the 12 lead electrocardiogram. The right chest leads do not add much to the diagnostic accuracy of the 12 lead electrocardiogram. Therefore, the risk of missing a diagnosis of acute myocardial infarction if the right chest leads are not examined is very small. But the right chest leads are useful for diagnosing the distribution of infarct between the right and the left ventricle. In patients with electrocardiographic inferior/posterior infarction, the right chest leads can identify those without ST elevation in V3R–V7R (predominantly left ventricular infarction), who have a similar prognosis to patients with anterior infarction, and those with ST elevation in V3R–V7R (extensive infarction of the right ventricle and minor infarction of the left ventricle) who have a much better prognosis.[21] None the less, cardiogenic shock can develop in such patients despite only slight impairment of the left ventricle. Early recognition of this infarct distribution by electrocardiography may be needed to ensure that these patients are treated appropriately.[22]

We conclude that involvement of the right ventricle during inferior/posterior infarction can be diagnosed with high accuracy by right chest leads V6R and V7R.

References

1 Sanders AO. coronary thrombosis with complete heart block and relative ventricular tachycardia. A case report. *Am Heart J* 1930–31;6:820–3.

2 Erhardt LR. Clinical and pathological observations in different types of acute myocardial infarction. *Acta Med Scand* 1974;suppl 560:1–78.

3 Braat SH, Gorgels APM, Bar FW, Wellens HJJ. Value of the ST-T segment in lead V4R in inferior wall acute myocardial infarction to predict the site of coronary arterial occlusion. *Am J Cardiol* 1988; **62**:140–2.

4 Lopez-Sendon J, Coma-Canella I, Alcasena S, Seoane J, Gamallo C. Electrocardiographic findings in acute right ventricular infarction: sensitivity and specificity of electrocardiographic alterations in right precordial leads V4R, V3R, V1, V2 and V3. *J Am Coll Cardiol* 1985;**6**:1273–9.

5 Morgera T, Alberti E, Silvestri F, Pandullo C, Della Mea MT, Camerini F. Right precordial ST and QRS changes in the diagnosis of right ventricular infarction. *Am Heart J* 1984;**108**:13–8.

6 Klein HO, Tordjman T, Ninio R, *et al.* The early recognition of right ventricular infarction: diagnostic accuracy of the electrocardiographic V4R lead. *Circulation* 1983;**67**:558–65.

7 Erhardt LR, Sjögren A, Wahlberg I. Single right-sided precordial lead in the diagnosis of right ventricular involvement in inferior myocardial infarction. *Am Heart J* 1976;**91**:571–6.

8 Braat SH, Brugada P, Dulk K, Ommen V, Wellens HJJ. Value of lead V4R for recognition of the infarct coronary artery in acute inferior myocardial infarction. *Am J Cardiol* 1984;**53**:1538–41.

9 Funk M. Diagnosis of right ventricular infarction with right precordial ECG leads. *Heart Lung* 1986;**15**: 562–71.

10 Braat SH, Brugada P, De Zwaan C, Coenegracht JM, Wellens HJJ. Value of electrocardiogram in diagnosing right ventricular involvement in patients with an acute inferior wall myocardial infarction. *Br Heart J* 1983;**49**:368–72.

11 Croft CH, Nicod P, Corbett JR, *et al.* Detection of acute right ventricular infarction by right precordial electrocardiography. *Am J Cardiol* 1982;**50**:421–7.

12 Forman MB, Wilson BH, Sheller JR, *et al.* Right ventricular hypertrophy is an important determinant of right ventricular infarction complicating acute inferior left ventricular infarction. *J Am Coll Cardiol* 1987;**10**:1180–7.

13 Carson W. Patterns of maximal spatial ST vector of S-T segment elevation in the right praecordial leads of the electrocardiogram in patients with acute inferior myocardial infarction. *Eur Heart J* 1988;**9**:962–8.

14 Andersen HR, Falk E, Nielsen D. Right ventricular infarction: frequency, size and topography in coronary heart disease. A prospective study comprising 107 consecutive autopsies from a coronary care unit. *J Am Coll Cardiol* 1987;**10**:1223–32.

15 Andersen HR, Falk E, Nielsen D. Clinical first myocardial infarction: coronary artery disease and old infarcts in 53 consecutive fatal cases from a coronary care unit. *Am J Cardiovasc Pathol* (in press).

16 Ideker RE, Hackel DB, McClees EC. Myocardial infarction: postmortem anatomic quantitation. In Wagner GS, ed. *Myocardial infarction: measurements and intervention.* Boston: Martinus Nijhoff, 1982: 347–71.

17 Rose GA, Blackburn H. Cardiovascular survey methods. *WHO Monogr Ser* No 56, 1968.

18 Andersen HR, Nielsen D, Hansen LG. The normal right chest electrocardiogram. *J Electrocardiol* 1987; **20**:27–32.

19 Rowlands DJ. *Understanding the electrocardiogram.* Manchester: Gask and Hawley, 1982.

20 Galen RS. Predictive value of laboratory tests. *Am J Cardiol* 1975;**36**:536–8.

21 Andersen HR, Nielsen D, Lund O, Falk E. Prognostic significance of right ventricular infarction diagnosed by ST elevation in right chest leads V3R to V7R. *Int J Cardiol* (in press).

22 Dell'Italia LJ, Starling MR, Blumhardt R, Lasher JC, O'Rouke RA. Comparative effects of volume loading, dobutamine, and nitroprusside in patients with predominant right ventricular infarction. *Circulation* 1985;72:1327–35.

Br Heart J 1989;61:521–8

Cold intolerance in patients with angina pectoris: effect of nifedipine and propranolol

I PEART, R E BULLOCK, C ALBERS, R J C HALL

From the Department of Cardiology, Royal Victoria Infirmary, Newcastle upon Tyne

SUMMARY Fifteen patients with chronic stable angina pectoris and a history of reduced exercise tolerance in cold weather (cold intolerance) underwent symptom limited treadmill exercise tests at 20°C and 0°C in a specially constructed cold chamber while taking no antianginal medication. Their mean time to onset of angina (5·8 *v* 4·2 min), to 1 mm ST depression (5·1 *v* 3·8 min), and to peak exercise (7·4 *v* 5·7 min) was significantly shorter on exercise at 0°C than at 20°C. The double product of heart rate and systolic blood pressure at each of these end points was the same in both exercise tests. Eight of these patients were treated with nifedipine 10 mg three times a day for two weeks and then with propranolol 40 mg three times a day for another two weeks. Repeat exercise testing was performed at the end of each two week treatment period. The mean time (SD) to peak exercise at the end of the nifedipine treatment period was 9·1 (2·0) min at 20°C and 8·5 (2·3) min at 0°C. The double product at peak exercise was the same for both exercise tests. At the end of the propranolol treatment period the mean time to peak exercise was significantly less at 0°C (7·8 (2·6) min) than at 20°C (8·9 (2·4) min). The double product at peak exercise was the same for both exercise tests but was significantly less than that on nifedipine.

Cold intolerance was shown in patients with a positive history by symptom limited treadmill exercise testing at 0°C. It persisted when they were treated with propranolol, albeit to a lesser extent, but not when they were treated with nifedipine.

Not infrequently patients with chronic stable angina pectoris complain that their symptoms are more easily provoked in cold weather (cold intolerance). Although we found that 60% of patients with angina pectoris[1] reported such cold intolerance it has proved very difficult to obtain objective evidence of this phenomenon. Indeed in one study only 50% of patients with a history of cold intolerance showed a decreased exercise tolerance in a cold environment.[2]

Various mechanisms have been suggested to explain the phenomenon, including a reflex increase in peripheral vascular resistance resulting in increased cardiac work,[3] and a reflex increase in coronary artery tone or even coronary artery spasm producing a reduction in coronary perfusion.[4 5]

Cold intolerance is seldom considered when decisions are made about the treatment of patients with chronic stable angina. β Blockers,[6] for instance, increase both peripheral and coronary vascular resistance and could theoretically, therefore, worsen cold intolerance. Calcium antagonists,[7] on the other hand, reduce both peripheral and coronary vascular resistance and may, thus, be a better choice of antianginal agent in patients with cold intolerance.

The present study was designed to look at three problems. Is it possible to show by exercise testing at 0°C and 20°C the phenomenon of cold intolerance in a group of patients with chronic stable angina pectoris? Do β blockers and calcium antagonists affect cold intolerance in different ways? Can simple observations of heart rate, blood pressure, and exercise tolerance shed light on the, at present, obscure mechanisms underlying the clinical phenomenon?

Patients and methods

PATIENTS

We studied 15 patients (four women and 11 men aged 40–60 (mean 49)) with a history of chronic stable angina pectoris who were not taking regular antianginal treatment apart from glyceryl trinitrate as required. All patients complained that their angina attacks were more frequent and more easily provoked in cold weather and at night. None had had an acute

Requests for reprints to Dr R J C Hall, Department of Cardiology, University Hospital of Wales, Heath Park, Cardiff CF4 4XW.

Accepted for publication 10 January 1989

myocardial infarction in the preceding six months and none had undergone coronary artery surgery. Patients with chronic obstructive airways disease were excluded. Informed consent was obtained from all patients.

EXERCISE TESTING

Exercise testing was undertaken in a specially built room with internal insulation, a securely fitted refrigerator door and a duct through which cold air entered the room to cool the room before, and to maintain the temperature during, the cold exercise tests. The room was cooled by a continuous flow of cold air during the night before the cold exercise tests. This ensured that the wall temperature of the room was also at 0°C. Exercise tests were performed at a room temperature of 18–20°C (warm exercise tests) and at 0°C (cold exercise tests). Temperatures were measured by thermocouples. During the cold exercise tests cold air was directed via the duct at the patient's face and trunk at a wind velocity of approximately 2 m/s. All monitoring and electrocardiographic recording equipment was moved out of the room for the cold exercise tests. During exercise testing these instruments were viewed through a window in the door. The treadmill was tested to ensure that there was no significant reduction in speed at 0°C compared with 20°C. For the cold exercise tests the patients wore their normal shoes with trousers or a skirt, and a T shirt covered by a warm, fibrepile anorak that was sleeveless to permit blood pressure recording.

All subjects underwent two preliminary treadmill exercise tests at room temperature (18–20°C) using a modified Bruce protocol (table 1) on different days to acquaint them with the equipment and procedure to ensure that their exercise tolerance (under baseline conditions) was reproducible and that time to peak exercise did not vary by more than 5% between tests. Exercise tests (including those during the pharmacological study) were performed at the same time each day and the patients were asked to abstain from smoking and eating for at least four hours before the exercise test. Patients were asked not to take any glyceryl trinitrate on the day of their exercise tests. After they were attached to the electrocardiograph they rested for 15 minutes before any measurements were taken or the exercise test was started.

For the study, the warm and cold exercise tests were performed on consecutive mornings, the order having been randomised. Eight patients had their warm exercise test first and seven patients had their cold exercise test first.

A standard 12 lead electrocardiogram and blood pressure on a mercury-random zero sphygmomanometer were recorded with the patient lying and standing at rest every minute during the exercise test, at peak exercise, and every minute after exercise until the electrocardiogram had returned to its resting appearance. Leads II, V2, and V5 were recorded continuously throughout all exercise tests. Facial, trunk, and forearm temperatures were monitored throughout the cold exercise tests. To exclude exercise induced asthma as a cause of symptoms a Vitalograph was used to record forced expiratory volume in one second and forced vital capacity both before and after exercise.

Table 1 *Exercise protocol*

Stage	*Speed (mph)*	*Gradient (%)*
½	1·7	5
1	1·7	10
2	2·5	12
3	3·4	14
4	4·2	16
5	5·0	18

1 mph = 1·6 k/h.

PHARMACOLOGICAL INTERVENTION

After we established that cold intolerance could be shown by the symptom limited exercise test at 0°C in the first seven patients, we treated the next eight patients (numbers 8–15 in table 3 and 1–8 in table 5) with nifedipine and propranolol in a single blind but not randomised trial. We treated these eight patients for two weeks with nifedipine 10 mg three times a day and repeated the warm (20°C) and cold (0°C) exercise tests at the end of the treatment period. Then we treated them with propranolol (40 mg three times a day) for a further two weeks and repeated the exercise tests.

DATA ANALYSIS

All exercise tests were symptom limited; before each test patients were asked to exercise until they felt that their angina was at a level that would normally cause them to stop during everyday activities. For each exercise test we noted the time of and the heart rate, blood pressure and double product (heart rate × systolic blood pressure) at the onset of angina, the development of 1 mm ST segment depression, and the termination of exercise. For the cold exercise tests the temperature of the cold room and each patient's facial, trunk, and forearm temperatures at peak exercise were recorded.

STATISTICAL ANALYSIS

Differences between variables were analysed for statistical significance by Student's paired t tests. The results are presented as mean time and the standard error of the mean of the differences in

Table 2 *Exercise test data (mean (SD)) for the 15 patients exercised at 0°C and 20°C on no antianginal medication*

	At rest		Angina onset	
	DP (× 10³) at 20°C	DP (× 10³) at 0°C	Min	DP (× 10³)
Warm (20°C) exercise test	10·9 (2·9)		5.80 (2·09)	24·0 (7·1)
p ⟶	NS		< 0·001	NS
Cold (0°C) exercise test	11·0 (3·0)	12·8 (3·4)	4·22 (1·57)	23·9 (7·2)
	p < 0·001	p < 0·001		

	1 mm ST depression		Peak exercise	
	Min	DP (× 10³)	Min	DP (× 10³)
Warm (20°C) exercise test	5·14 (2.33)	21·5 (6·4)	7·37 (2·26)	26·1 (8·0)
p ⟶	< 0·005	NS	< 0·001	NS
Cold (0°C) exercise test	3·77 (1·58)	21·7 (6·7)	5·73 (2·01)	25·9 (7·5)

DP, double product of heart rate × blood pressure.
DP at 20°C for cold exercise test is DP before entry to cold room.

exercise time, with the 95% confidence interval. The data in the tables are means (SD).

Results

NO TREATMENT

Table 2 shows the group data for the 15 patients exercised at 0°C and 20°C on no antianginal medication. Table 3 and the figure show the data for individual patients. There was no difference in the resting double product at room temperature (20°C) before either the warm or cold exercise tests (10·9 *v* 11·0 (0·27), 95% CI −0·48 to 0·68). After one minute in the cold room, before the cold exercise test, there was a significant increase in the double product (11·0 *v* 12·8 (0·23), 95% CI 1·31 to 2·29; p < 0·001) but no change in the heart rate (83·4 *v* 85·3 (1·28) beats/min, 95% CI −0·85 to 4·65). The important effect, therefore, was on the systolic blood pressure. The exercise time to onset of angina (5·8 *v* 4·2 (0·31) min, 95% CI 0·94 to 2·26; 27·6% reduction; p < 0·001), to the development of 1 mm ST depression (5·1 *v* 3·8 (0·32) min, 95% CI 0·61 to 2·0; 25·5% reduction; p < 0·005), and to peak exercise (7·4 *v* 5·7 (0·24) min, 95% CI 1·19 to 2·21; 23·0% reduction; p < 0·001) all decreased significantly in the cold. The double product at each of these points was the same in the cold as in the warm although obviously it was reached more quickly.

There was no significant change in either forced expiratory volume in one second or forced vital capacity in any patient after any of the exercise tests.

PHARMACOLOGICAL STUDY

Tables 4 and 5 summarise the exercise test data obtained in the eight patients in the pharmacological study. Before treatment, cold intolerance had been shown in this group of patients. Their mean time to onset of angina (5·4 *v* 3·5 (0·47) min, 95% CI 0·79 to 3·01; p < 0·01), to 1 mm ST depression (4·5 *v* 3·1 (0·44) min, 95% CI 0·36 to 2·44; p < 0·05), and to peak exercise (6·8 *v* 5·0 (0·25) min, 95% CI 1·21 to 2·39; p < 0·001) all decreased significantly in the cold.

NO TREATMENT VERSUS NIFEDIPINE (TABLE 4)

After two weeks' treatment with nifedipine there were significant increases in the exercise time to onset of angina (5·4 *v* 7·8 (0·56) min, 95% CI 1·08 to 3·72 at 20°C; p < 0·01; 3·5 *v* 7·2 (0·58) min, 95% CI 2·33 to 5·07 at 0°C; p < 0·001) and to peak exercise (6·8 *v* 9·1 (0·53) min, 95% CI 1·05 to 3·55 at 20°C; p < 0·02; 5·0 *v* 8·5 (0·66) min, 95% CI 1·94 to 5·06 at 0°C; p < 0·01). The time to 1 mm ST depression did not increase in the warm (20°C) (4·5 *v* 5·8 (1·3) min, 95% CI −1·77 to 4·37; NS) but was significantly longer in the cold (0°C) (3·1 *v* 5·3 (0·86) min, 95% CI 0·17 to 4·23; p < 0·02). At the end of the nifedipine

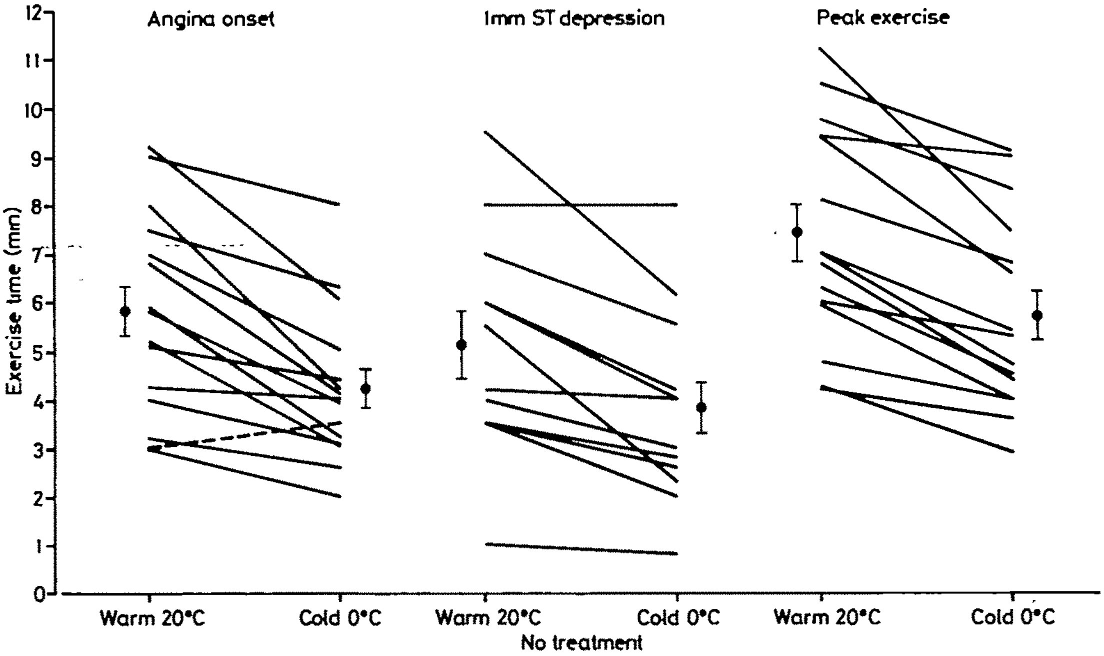


Figure *Exercise time (in minutes) to onset of angina, to 1 mm ST depression, and to peak exercise in 15 patients on no antianginal medication at 20°C and at 0°C. Mean time (SEM) to onset of angina ($p < 0{\cdot}001$), to 1 mm ST depression ($p < 0{\cdot}005$), and to peak exercise ($p < 0{\cdot}001$) were all significantly reduced at 0°C.*

treatment period there was no cold intolerance in terms of time to peak exercise (9·1 min at 20°C *v* 8·5 min at 0°C (0·42) min, 95% CI −0·4 to 1·6; NS). The double product at the onset of angina, at 1 mm ST depression, and at peak exercise was the same for both the warm and cold exercise tests on nifedipine, and the double product at these three stages was the same on nifedipine treatment as it was without treatment.

NO TREATMENT VERSUS PROPRANOLOL (TABLE 4)

After two weeks' treatment with propranolol there were significant increases in the exercise time to onset of angina (5·4 *v* 7·1 (0·62) min, 95% CI 0·23 to 3·17 at 20°C; $p < 0{\cdot}05$; 3·5 *v* 6·2 (0·66) min, 95% CI 1·14 to 4·26 at 0°C; $p < 0{\cdot}01$), to 1 mm ST depression 4·5 *v* 6·5 (0·68) min, 95% CI 0·39 to 3·61 at 20°C; $p < 0{\cdot}05$; 3·1 *v* 5·6 (0·45) min, 95% CI 1·44 to 3·56 at 0°C; $p < 0{\cdot}01$), and to peak exercise (6·8 *v* 8·9 (0·52) min, 95% CI 0·87 to 3·33 at 20°C; $p < 0{\cdot}01$; 5·0 *v* 7·8 (0·56) min, 95% CI 1·48 to 4·12 at 0°C; $p < 0{\cdot}01$). Cold intolerance as judged by the time to peak exercise was still demonstrable at the end of the propranolol treatment period (8·9 *v* 7·8 (0·23) min, 95% CI 0·56 to 1·64; $p < 0{\cdot}01$) although to a lesser extent than before treatment (26·5% *v* 12·3% reduction in exercise tolerance). The double product was the same at onset of angina, at 1 mm ST depression, and at peak exercise in both the warm and cold exercise tests on propranolol. During treatment with propranolol, however, the double product was significantly less at all points during exercise compared with the exercise tests on no treatment ($p < 0{\cdot}01$).

NIFEDIPINE VERSUS PROPRANOLOL

There was no significant difference between the exercise time to onset of angina, to 1 mm ST depression, or to peak exercise on nifedipine or on propranolol. The double product, however, was significantly less at all points during exercise both in the warm and in the cold on propranolol as compared with nifedipine ($p < 0{\cdot}01$).

Discussion

A fall in the environmental temperature can have two effects on patients with ischaemic heart disease. The most common and immediately apparent is a considerable deterioration in their symptoms; Heberden first observed this in his classic description of angina pectoris.[8] Over half of our patients with chronic

Table 3 *Exercise test data for the 15 patients exercised at 0°C and 20°C on no antianginal medication*

		*At rest**			*Angina onset*				*1 mm ST depression*				*Peak exercise*			
No	*W/C*	*HR*	*BP*	*DP* (× 10^3)	*Min*	*HR*	*BP*	*DP* (× 10^3)	*Min*	*HR*	*BP*	*DP* (× 10^3)	*Min*	*HR*	*BP*	*DP* (× 10^3)
1	W	63	100	6 3	4 25	110	110	12 1	4 2	110	120	13·2	6 0	112	112	12 5
	C	62	90	5·6	4 0	110	120	13 2	4 0	110	124	13·6	5·3	112	130	14·6
	C+1	67	104	6 9												
2	W	96	176	16 9	5·1	130	204	26 5	3·5	122	190	23 2	8·1	148	216	31·9
	C	92	176	16 2	4 4	130	200	26 0	2 0	122	190	23 2	6 8	140	216	30·2
	C+1	96	190	18 2												
3	W	76	146	11 1	5 8	108	160	17 3	6 0	108	160	17 3	6 25	105	166	17 4
	C	64	156	9 9	3 9	106	160	16 9	4 2	108	160	17 3	4·5	109	156	17 0
	C+1	68	170	11 5												
4	W	88	130	11 4	7 5	140	180	25·2	8 0	148	180	26 6	10 5	175	200	35 0
	C	92	120	11 0	6 3	152	180	27 3	8 0	160	180	28 8	9·1	180	190	34 2
	C+1	106	130	13 8												
5	W	78	154	12 0	9 2	170	212	36 0	9 5	170	212	36·0	11 2	180	216	38 9
	C	82	144	11 8	6 0	170	210	35·7	6·1	170	220	37·4	7·4	170	222	37 7
	C+1	90	170	15·3												
6†	W	63	120	7 6	9 0	160	160	25 6	—	—	—	—	9 4	160	160	25 6
	C	74	122	9 0	8 0	160	170	27 2	—	—	—	—	9 0	160	174	27·8
	C+1	66	136	8 9												
7	W	64	124	7 9	3 2	100	140	14 0	3 5	102	144	14 7	4·75	107	150	16 0
	C	68	110	7 5	2·6	112	150	16·8	2 6	112	150	16 8	4·0	120	142	17 0
	C+1	70	140	9 8												
8	W	70	130	9 1	8 0	155	172	26·7	5 5	130	164	21 3	9·4	158	170	26 9
	C	74	138	10 2	4 2	146	180	26·2	2 3	124	174	21·6	6 6	150	176	26·4
	C+1	80	166	13 2												
9	W	68	136	9·2	7 0	144	162	23·3	7 0	144	162	23 3	9·75	150	176	26·4
	C	70	120	8 4	5 0	120	176	21 1	5 5	120	176	21 1	8 3	140	180	25 2
	C+1	72	136	9 7												
10	W	89	128	11 4	5 9	146	172	25·1	4 0	140	156	21 8	7 0	150	176	26·4
	C	96	144	13 8	3 2	130	174	22·6	3·0	130	174	22 6	5·4	140	192	26 9
	C+1	96	155	14 9												
11	W	82	136	11 1	4 0	106	160	16 9	1 0	94	150	14·1	5 9	104	172	17·9
	C	76	138	10 5	3 1	100	162	16 2	0 8	96	150	14 4	4 0	108	178	19 2
	C+1	80	144	11 5												
12†	W	94	140	13 1	3 0	148	196	29 0	—	—	—	—	4 2	150	212	31 8
	C	92	150	13 8	3 5	144	208	29 9	—	—	—	—	3 6	144	210	30·2
	C+1	90	162	14 6												
13†	W	104	152	15 8	6 8	176	210	36 9	—	—	—	—	7 0	176	212	37 3
	C	104	160	16 6	4 1	180	210	37 8	—	—	—	—	4·7	180	212	38 2
	C+1	108	176	19 0												
14	W	96	118	11 3	3 0	124	162	20 1	3 5	126	164	20·7	4 25	120	166	19·9
	C	80	130	10 4	2 0	106	160	16 9	2 8	112	160	17 9	2 9	112	162	18 1
	C+1	78	136	10 6												
15	W	66	150	9 9	5·2	140	176	24 6	6 0	144	180	25·9	6 8	150	182	27·3
	C	75	146	10 9	3 0	140	180	25 2	4·0	144	182	26·2	4 4	140	190	26 6
	C+1	78	176	13 7												

*Values before entry into cold room (0°C).

†No significant ST depression in three patients.

HR, heart rate, BP, systolic blood pressure (mm Hg); DP, double product of heart rate × blood pressure; W, warm (20°C) exercise test; C, cold (0°C) exercise test, C+1 = HR, BP, DP after 1 min in cold room (0°C) before starting exercise test.

stable angina pectoris commented that in cold weather not only did the frequency and severity of their symptoms increase but also that symptoms were more easily provoked.[1] Cold weather also causes an overall increase in cardiovascular mortality.[9]

Several studies have examined the relation between environmental temperature and cardiovascular mortality.[10–12] In 1966 Rose analysed the seasonal distribution of death and reinfarction in the Medical Research Council trial of long term anticoagulant treatment after acute myocardial infarction and showed that reinfarction was almost twice as common in December as in June and that the "winter excess of deaths in any particular year was very highly correlated with coldness".[11] He concluded that changes in temperature were responsible for most of the short term fluctuations in mortality from ischaemic heart disease. Further evidence from Canada confirmed the importance of a sudden drop in temperature in increasing deaths from ischaemic heart disease, especially when the cold stimulus was accompanied by exercise, such as clearing snow.[13] In the Canadian study the daily rate of sudden death increased during "cold snaps" (defined as days when the temperature was at least 4·4°C lower than the previous day) and around the time of heavy snow-

Table 4 *Exercise test data (mean (SD)) for the eight patients in the pharmacological study. Data are presented for exercise testing before treatment, after two weeks on nifedipine, and after two weeks on propranolol*

	No treatment			*Nifedipine*			*Propranolol*		
	Time to:			*Time to:*			*Time to:*		
	AP onset (min)	*1 mm ST↓ (min)*	*Peak exercise (min)*	*AP onset (min)*	*1 mm ST↓ (min)*	*Peak exercise (min)*	*AP onset (min)*	*1 mm ST↓ (min)*	*Peak exercise (min)*
Warm (20°C) exercise test	5·4 (1·9)	4·5 (2·1)	6·8 (2·1)	7·8 (2·2)	5·8 (0·8)	9·1 (2·0)	7·1 (2·1)	6·5 (1·6)	8·9 (2·4)
p →	*	**	***	****			****	**	*
Cold (0°C) exercise test	3·5 (0·9)	3·1 (1·6)	5·0 (1·7)	7·2 (2·2)	5·3 (1·8)	8·5 (2·3)	6·2 (2·2)	5·6 (1·9)	7·8 (2·6)
	DP ($\times 10^3$)	DP ($\times 10^3$)	DP ($\times 10^3$)	DP ($\times 10^3$)	DP ($\times 10^3$)	DP ($\times 10^3$)	DP ($\times 10^3$)	DP ($\times 10^3$)	(DP $\times 10^3$)
Warm (20°C) exercise test	25·3 (6·0)	21·2 (3·9)	26·7 (6·1)	25·2 (5·5)	21·7 (4·1)	27·8 (4·9)	16·1 (3·6)	16·1 (3·2)	17·5 (4·3)
Cold (0°C) exercise test	24·5 (7·1)	20·6 (4·1)	26·3 (6·3)	26·0 (3·5)	22·9 (3·7)	27·7 (3·6)	16·3 (3·4)	15·9 (3·3)	17·5 (4·2)

*$p < 0·01$; **$p < 0·05$; ***$p < 0·001$; ****$p < 0·02$.
AP, angina.

falls, particularly in men under 65 years of age. The reasons for the increased mortality and the mechanisms by which it occurs are unknown and beyond the scope of our study, although in at least one study unaccustomed exertion seemed to play a part.[13]

Despite the frequency with which patients complain of deteriorating symptoms in winter, no studies have attempted to simulate the environmental conditions experienced by these patients on an average winter's day in Britain or have examined the effects of antianginal treatment. In part this is because it is difficult to obtain objective evidence of cold intolerance in individual patients. Two studies from Sweden have investigated certain aspects of the problem but at the much lower temperatures found in Sweden.[2, 14] Lassvik and Areskog studied 17 men with angina pectoris and cold intolerance who performed submaximal bicycle exercise tests at 20°C and −10°C.[2] Despite their history of cold intolerance, the phenomenon could only be shown in 59% and the reduction in exercise tolerance was only about 10%, a much smaller reduction than would be expected from their history. The failure to show the effect may have related to the fact that the laboratory procedure failed

Table 5 *Exercise test data for the eight patients involved in the pharmacological study*

		No treatment							*Nifedipine*						
			AP onset		*1 mm ST↓*		*Peak exercise*			*AP onset*		*1 mm ST↓*		*Peak exercise*	
		Rest DP (× 10³)	*min*	*DP (× 10³)*	*min*	*DP (× 10³)*	*min*	*DP (× 10³)*	*Rest DP (× 10³)*	*min*	*DP (× 10³)*	*min*	*DP (× 10³)*	*min*	*DP (× 1*
1	W	9·1	8·0	26·7	5·5	21·3	9·4	26·9	15·4	10·1	33·3	5·5	26·5	11·2	33·3
	C	13·2	4·2	26·2	2·3	21·6	6·6	26·4	13·9	9·2	28·4	4·2	22·6	10·0	29·9
2	W	9·2	7·0	23·3	7·0	23·3	9·75	26·4	8·5	9·0	26·1	—	—	9·9	30·6
	C	9·7	5·0	21·1	5·5	21·1	8·3	25·2	9·5	8·0	25·8	—	—	9·6	29·3
3	W	11·4	5·9	25·1	4·0	21·8	7·0	26·4	11·4	9·4	24·0	7·0	20·7	10·5	28·5
	C	14·9	3·2	22·6	3·0	22·6	5·4	26·9	14·3	9·2	27·8	8·0	27·3	10·7	30·1
4	W	11·1	4·0	16·9	1·0	14·1	5·9	17·9	12·8	8·5	20·0	5·6	16·6	11·2	25·2
	C	11·5	3·1	16·2	0·8	14·4	4·0	19·2	11·1	7·7	22·7	4·0	18·3	9·8	25·5
5	W	13·1	3·0	29·0	—	—	4·2	31·8	12·5	7·2	25·0	—	—	7·5	25·6
	C	14·6	3·5	29·9	—	—	3·6	30·2	13·3	6·2	26·0	—	—	7·0	26·9
6	W	15·8	6·8	36·9	—	—	7·0	37·3	14·7	9·0	32·3	—	—	9·5	34·6
	C	19·0	4·1	37·8	—	—	4·7	38·2	19·5	9·0	31·0	—	—	10·0	32·7
7	W	11·3	3·0	20·1	3·5	20·7	4·25	19·9	11·1	4·0	17·5	—	—	6·9	20·0
	C	10·6	2·0	16·9	2·8	17·9	2·9	18·1	12·1	3·2	19·8	—	—	4·0	21·0
8	W	9·9	5·2	24·6	6·0	25·9	6·8	27·3	11·2	5·0	23·0	5·0	22·9	6·0	24·7
	C	13·7	3·0	25·2	4·0	26·2	4·4	26·6	11·7	5·2	26·7	5·0	23·5	6·6	26·0

DP, double product of heart rate × blood pressure; AP, angina; W, warm exercise test (20°C); C, cold exercise test (0°C): figure for DP at rest DP after 1 min in cold room; —, no significant ST depression.

to reproduce the real life situation, ignoring important factors such as clothing, wind, etc.

The two mechanisms invoked to account for the phenomenon of cold intolerance are reflex increases in peripheral vascular resistance producing increased cardiac work,[3] and reflex increases in coronary vascular resistance producing reduced coronary perfusion.[4 5] Published studies suggest that the effect on peripheral vascular resistance is more important. In normal subjects and patients with angina pectoris exposure to cold has been shown to result in peripheral vasoconstriction[15] and a rise in blood pressure.[16] Hayward *et al* showed that blowing cold air on to the face produced bradycardia and an increase in forearm vascular resistance,[3] a response thought to be mediated via the vagus nerve. The same response, however, was not seen if the cold air was applied to the abdomen. Lassvik and Areskog provided further evidence of the importance of increased peripheral vascular resistance by showing that blood pressure in patients with angina pectoris was significantly higher throughout exercise in the cold.[2] In the present study we showed that even a short exposure to cold (one minute before the start of the cold exercise test) is sufficient to increase blood pressure ($p < 0\cdot001$) and the double product ($p < 0\cdot01$) significantly, while heart rate remained unchanged. This is, almost certainly, related to a reflex increase in peripheral vascular resistance. Although an increase in cardiac output might produce similar findings this is unlikely to be the case because an earlier study showed regional deterioration in left ventricular function in patients with ischaemic heart disease on exposure to cold.[17] At each minute stage of all of the cold exercise tests both blood pressure and double product were significantly greater than values attained during the warm exercise tests. Blood pressure and double product at the onset of angina, at 1 mm ST depression, and at peak exercise were the same during the warm and cold exercise tests (table 3) although these values were achieved much earlier in the cold. The overall reduction in exercise tolerance in these patients is therefore related to increased cardiac work at any particular stage of the cold exercise tests as measured by the double product, which is a good index of myocardial oxygen consumption.[18]

Propranolol						
	AP onset		*1 mm ST ↓*		*Peak exercise*	
Rest DP (× 10³)	*min*	*DP (× 10³)*	*min*	*DP (× 10³)*	*min*	*DP (× 10³)*
8·3	10·1	21·8	7·0	17·6	13·3	25·0
9·7	8·2	19·3	5·8	15·8	12·2	24·6
5·2	8·5	16·5	7·0	14·6	10·0	18·5
6·3	8·5	17·0	7·0	15·2	9·6	17·3
8·1	9·7	17·6	8·0	16·6	10·2	17·6
9·5	9·2	19·0	7·2	17·9	9·4	18·7
7·9	7·5	12·9	4·0	11·1	9·5	13·2
7·6	6·0	11·2	3·5	10·4	7·4	12·7
7·1	6·1	13·2	—	—	7·0	14·3
7·4	4·3	13·6	—	—	5·3	15·3
12·2	5·7	20·9	5·0	20·7	7·25	21·9
12·0	4·6	20·9	3·0	20·3	6·8	21·9
12·0	4·5	13·2	—	—	5·5	12·6
10·8	3·1	13·3	—	—	3·75	13·1
7·3	5·0	13·3	8·0	16·4	8·3	17·3
9·6	5·4	16·0	7·3	16·0	7·7	16·0

The importance of coronary vascular resistance in determining cold intolerance is more difficult to assess because much of the work on coronary vascular resistance used a painful, non-physiological stimulus, the cold pressor test.[19 20] Nevertheless, this method showed an increase in coronary vascular resistance during cold stimulation, which was inhibited by nifedipine.[21 22] This effect is relevant to the treatment of coronary artery spasm.

In considering treatment for patients with cold intolerance it is helpful to remember the mechanisms of action of commonly used antianginal agents. The β blockers, particularly non-cardioselective ones such as propranolol, increase peripheral vascular resistance by leaving peripheral vasoconstrictor forces unopposed, and they also increase coronary vascular resistance, thus reducing coronary perfusion.[6] Despite these effects some recommend an increased dose in winter.[23] Calcium antagonists such as nifedipine, on the other hand, act mainly on vascular smooth muscle[7] both in peripheral arterioles where they reduce peripheral vascular resistance and in coronary arteries where they produce dilatation and an increase in coronary blood flow and oxygen to the myocardium. These latter agents may, therefore, have advantages over β blockers in the treatment of cold intolerant patients with angina.

We showed significant increases in exercise tolerance in both the warm and the cold when patients were treated with propranolol or nifedipine, and there was no significant difference in overall exercise tolerance on either drug. Whereas we were unable to show cold intolerance in patients treated with nifedipine it was still evident with propranolol, albeit to a lesser extent than when no treatment was given. We did not investigate the value of nitrates in such patients, but a small study from Norway of bicycle ergometry found that when glyceryl trinitrate was given to patients before they cycled the work capacity in the cold (−17°C) increased to levels obtained at room temperature (18°C) and that this was mainly due to a decrease in the systolic blood pressure during cold exercise on treatment.[24] One explanation for the reduced systolic blood pressure would be a decrease in peripheral vascular resistance mediated by nitrate induced vasodilatation. Nitrates, however, are important venodilators and this action, by reducing preload, may lead to a reduction in systolic blood pressure by reducing cardiac output.

In conclusion, therefore, the phenomenon of cold intolerance can be shown at 0°C by symptom limited treadmill exercise testing, and the haemodynamic data obtained suggest that increases in peripheral vascular resistance are the major determinant of reduced exercise tolerance. There is little difference between nifedipine and propranolol but present evidence suggests that increased doses of calcium antagonists or nitrates would be useful in cold intolerant patients in the winter.

We thank the British Heart Foundation for providing the cold room, the National Heart Research Fund who supported IP, the Northern Regional Health Authority who supported REB, and Bayer Pharmaceuticals who supported CA.

References

1 Hall RJC, Bullock RE, Albers C. The effect of cold on patients with angina pectoris—a review. *Postgrad Med J* 1983;**59**(suppl 2):55–7.

2 Lassvik CT, Areskog N-H. Angina in cold environment. Reactions to exercise. *Br Heart J* 1979;**42**: 396–401.

3 Hayward JM, Holmes WF, Gooden BA. Cardiovascular responses in man to a stream of cold air. *Cardiovasc Res* 1976;**10**:691–6.

4 Gunther S, Green L, Muller JE, Mudge GH, Grossman W. Inappropriate coronary vasoconstriction in patients with coronary artery disease: a role for nifedipine? *Am J Cardiol* 1979;**44**:793–7.

5 Feldman RL, Whittle JL, Pepine CJ, Conti CR. Regional coronary angiographic observations during cold stimulation in patients with exertional chest pain: comparison of diameter responses in normal and fixed stenotic vessels. *Am Heart J* 1981;**102**:822–30.

6 Gunnells JC. Treatment of systemic hypertension. In: Hurst JW, ed. *The heart*. 5th ed. New York: McGraw-Hill, 1982:1196–220.

7 Stone DL, Stephens JD, Banim SO. Coronary haemodynamic effects of nifedipine: comparison with glyceryl trinitrate. *Br Heart J* 1983;**49**:442–6.

8 Heberden W. Some account of a disorder of the breast. *Medical Transactions of the Royal College of Physicians of London* 1772;**2**:59–67.

9 Dunnigan MG, Harland WA. Seasonal incidence and mortality of ischaemic heart disease. *Lancet* 1970; **ii**:793–7.

10 Bainton D, Moore F, Sweetnam P. Temperature and deaths from ischaemic heart disease. *Br J Prev Soc Med* 1977;**31**:49–53.

11 Rose G. Cold weather and ischaemic heart disease. *Br J Prev Soc Med* 1966;**20**:97–100.

12 Baker-Blocker A. Winter weather and cardiovascular mortality in Minneapolis—St. Paul. *Am J Public Health* 1982;**72**:261–5.

13 Anderson TW, Rochard C. Cold snaps, snowfall and sudden death from ischaemic heart disease. *Can Med Assoc J* 1979;**121**:1580–3.

14 Backman C, Holm S, Linderholm H. Reaction to cold of patients with coronary insufficiency. *Ups J Med Sci* 1979;**84**:181–7.

15 Epstein SE, Stampfer M, Beiser GD, Goldstein RE, Braunwald E. Effects of a reduction in environmental temperature on the circulatory response to exercise in man. Implications concerning angina pectoris. *N Engl J Med* 1969;**280**:7–11.

16 Brennan PJ, Greenberg G, Miall W, Thompson SG. Seasonal variation in arterial blood pressure. *Br Med J* 1982;**285**:919–23.

17 Manyari DE, Nolewajka AJ, Purves P, Donner A, Kostuk WJ. Comparative value of the cold pressor test and supine bicycle exercise to detect subjects with coronary artery disease using radionuclide ventriculography. *Circulation* 1982;**65**:571–9.

18 Gobel FL, Nordstrom LA, Nelson RR, Jorgensen CR, Wang Y. The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation* 1978; **57**:549–56.

19 Raizner AE, Chahine RA, Ishimori T, *et al*. Provocation of coronary artery spasm by the cold pressor test. Haemodynamic, arteriographic and quantitative angiographic observations. *Circulation* 1980;**62**: 925–32.

20 Malacoff RF, Mudge GH, Holman BL, Idoine J, Bifolck L, Cohn PF. Effect of the cold pressor test on regional myocardial blood flow in patients with coronary artery disease. *Am Heart J* 1983;**106**:78–84.

21 De Servi S, Mussini A, Specchia G, *et al*. Effects of nifedipine on coronary blood flow and coronary resistance during cold pressor test and ischaemic exercise in patients with coronary artery disease. *Eur Heart J* 1980;**1**(suppl B):43–7.

22 Goldhaber SZ, White MD, Holman BL, *et al*. Prevention by nifedipine of cold pressor induced decrease in left ventricular ejection fraction. *J Am Coll Cardiol* 1983;**1**:1512–7.

23 Anonymous. Cold and the heart. *Br Med J* 1974;**iii**:430.

24 Stanghelle JK, Nilsson S. Angina pectoris and the cold. *Int Rehabil Med* 1983;**5**:189–91.

Br Heart J 1989;61:529–39

Clinical, haemodynamic, and pharmacological effects of withdrawal and reintroduction of digoxin in patients with heart failure in sinus rhythm after long term treatment

S E PUGH, N J WHITE, J K ARONSON, D G GRAHAME-SMITH, J G BLOOMFIELD

From the Medical Research Council Unit and University Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford

SUMMARY A randomised, double blind, placebo controlled, crossover study of digoxin withdrawal and reintroduction was carried out over two periods of eight weeks each after long term treatment. Forty four patients with stable heart failure in sinus rhythm and plasma digoxin concentrations over 0·8 ng/ml were studied. Their progress was assessed by clinical criteria, by haemodynamic measurements (systolic time intervals and echocardiography), and by pharmacological measurements of erythrocytic sodium pump numbers and activity. After withdrawal of digoxin clinical deterioration occurred in only 25% of the patients. Furthermore, in only 9% of cases was digoxin reintroduction thought to be necessary. There was deterioration in only 11% of the patients during digoxin treatment. Deterioration during digoxin withdrawal was accompanied by changes in systolic time intervals, but similar, albeit smaller changes in systolic time intervals also occurred in patients with no deterioration. Deterioration was accompanied by changes in the pharmacological effects of digoxin on the erythrocytes, consistent with a loss of effect, and these changes did not occur in those who did not deteriorate. The occurrence of deterioration could not be predicted by any clinical, haemodynamic, or pharmacological measurements made before withdrawal.

When William Withering first used digitalis in the successful treatment of dropsy over 200 years ago, his practice was to give it for short periods of time.[1] This century the usefulness of digitalis as a positive inotropic drug in the treatment of heart failure was rediscovered, but it has been modern practice to use it for indefinite periods.

In recent years, however, the practice of continuing treatment indefinitely with digitalis in heart failure in sinus rhythm has been questioned. For example, in several studies it has been shown that most patients do not deteriorate clinically when digitalis is withdrawn after long term treatment.[2 3] Furthermore, some have shown that systolic time intervals, and other measures of haemodynamic function, do not change in patients whose clinical state does not deteriorate after withdrawal,[4–6] although this finding has not been confirmed by others.[7–10] In addition, we and others have shown that the cellular pharmacological effects of digoxin, demonstrable in the erythrocytes of patients on short term digoxin treatment, are not found in patients on long term treatment, suggesting tolerance to the pharmacological effects of digoxin.[11 12]

We decided, therefore, to carry out a randomised double blind, placebo controlled, crossover study of the effects of withdrawal and reintroduction of digoxin after long term treatment for heart failure in sinus rhythm, investigating simultaneously a range of different measures of the effects of digoxin clinically, haemodynamically, and pharmacologically. Our purposes were to determine the relations among these different levels of effect of digoxin (fig 1) and whether any of these measurements could be used to

Author for correspondence: Dr J K Aronson, MRC Clinical Pharmacology Unit, University Department of Clinical Pharmacology, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE.

Accepted for publication 20 January 1989

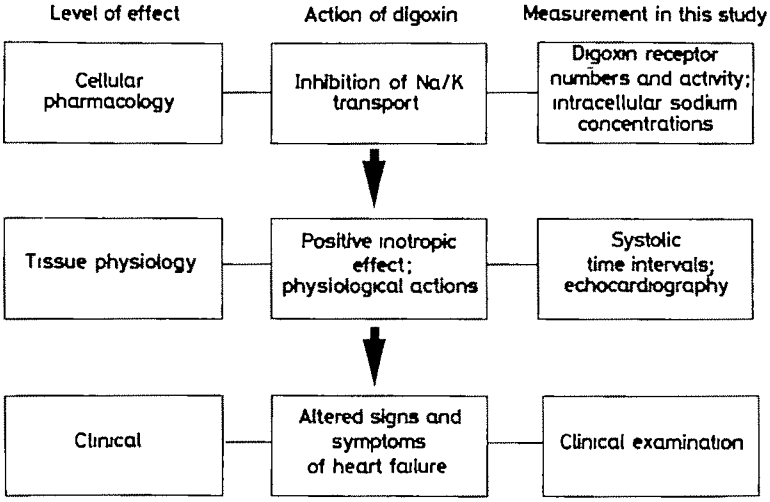

Level of effect
Action of digoxin
Measurement in this study
Cellular pharmacology
Inhibition of Na/K transport
Digoxin receptor numbers and activity; intracellular sodium concentrations
Tissue physiology
Positive inotropic effect; physiological actions
Systolic time intervals; echocardiography
Clinical
Altered signs and symptoms of heart failure
Clinical examination

Fig 1 *Different levels at which a drug may act in producing its therapeutic effect are shown on the left. A pharmacological effect at a cellular level is translated into a physiological effect, which in turn results in a clinical effect. The corresponding pharmacological, physiological (haemodynamic), and clinical effects of digoxin are shown in the centre column. The corresponding methods used in this study to investigate each of these levels of the action of digoxin are shown on the right.*

predict the clinical outcome after the withdrawal of digoxin.

The study was given the approval of the local ethics committee.

Patients and methods

PATIENTS

We studied 44 patients, all of whom fulfilled the following criteria: (*a*) digitalised for heart failure in sinus rhythm; (*b*) taking digoxin (Lanoxin, Wellcome) for at least three months; (*c*) no clinical evidence of digitalis toxicity; (*d*) steady state plasma digoxin concentrations (at least six hours after the previous dose) $\geqslant 0{\cdot}8$ ng/ml (1·0 nmol/l) and $\leqslant 2{\cdot}0$ ng/ml (2·6 nmol/l).

Table 1 shows the patients' ages, sex distribution, causes of heart failure, duration of treatment with digoxin, and other drug treatments.

Criteria for exclusion were: (*a*) atrial fibrillation; (*b*) plasma digoxin concentration $<0{\cdot}8$ ng/ml or $>2{\cdot}0$ ng/ml; (*c*) clinical evidence of fluid retention; (*d*) recent acute myocardial infarction (<3 months before).

Table 1 *Ages, sex distribution, causes of heart failure, duration of digoxin treatment, and other drug treatments at the start of the study*

			Deteriorators	
	Total	*Non-deteriorators*	*Placebo*	*Digoxin*
Number	44	28	11	5
Age (y) (median and range)	62 (39–76)	64 (39–76)	63 (53–76)	60 (39–70)
Male:female	32:12	22:6	7:4	3:2
Causes of heart failure:				
Ischaemic heart disease	27	20	5	2
Mitral valve disease	7	2	3	2
Aortic valve disease	8	5	2	1
Cardiomyopathy (dilated)	1	0	1	0
Hypertension	1	1	0	0
Duration of digoxin treatment (mnth) (median and range)	24 (3–258)	25 (3–258)	19 (3–108)	54 (7–120)
Other drug treatment:				
Diuretics	33 (75%)	19 (68%)	10 (91%)	4 (80%)
β adrenoceptor antagonists	9 (20%)	7 (25%)	1 (9%)	1 (20%)
Vasodilators	4 (9%)	3 (11%)	1 (9%)	0 (0%)

There were no exclusions based on other drug treatment, and wherever possible other drugs were continued in unchanging dosages throughout the study. Dosages of diuretics were increased during periods of deterioration when indicated (see Results).

DESIGN OF THE STUDY

Figure 2 shows the study design. After the initial assessment the patients were randomised to treatment with either their usual dosage of digoxin (Lanoxin) or to an equal number of matched placebo tablets. After eight weeks of continuous treatment (period 1) the alternative treatment was given and continued for a further eight weeks (period 2). All the patients were then given digoxin again for a final eight weeks (period 3). We have designated those patients who were randomised to placebo first as group 1 and those who were randomised to digoxin first as group 2.

When patients switched from placebo to digoxin treatment they were given three times the usual dose of digoxin on the first day only, as a loading dose. When they switched from digoxin to placebo extra placebo tablets were given to mimic a loading dose. Patients who "switched" from digoxin in period 2 to digoxin in period 3 were given their normal dose of digoxin on the first day of period 3 plus extra placebo tablets to mimic a loading dose. The issue of the tablets was controlled by the members of the pharmacy in the John Radcliffe Hospital, and the principal clinical investigators (SEP and NJW) were at all times blind to the order of the treatments. Clinical assessment was carried out both before randomisation and at weeks 1, 2, 4, 6, and 8 during each treatment period (fig 2). At the initial visit and at the first and eighth weeks of each treatment period (bold arrows in fig 2) the following investigations were made: full clinical assessment (history and examination); exercise test; measurement of systolic time intervals; echocardiography; blood tests (plasma digoxin concentration, erythrocyte cation transport receptor numbers and activity, and intra-erythrocytic sodium concentration). At the second, fourth, and sixth weeks of each visit (light arrows in fig 2) an interim assessment was made as follows: full clinical assessment; systolic time intervals; plasma digoxin concentration.

In the case of patients whose clinical condition deteriorated during the study a decision was made either to initiate or change diuretic treatment or to withdraw the patient from the study. One of us (JKA), who was blind to the order of treatments, was responsible for assessing what to do at times of apparent clinical deterioration, and for communicating between the blinded and non-blinded investigators, breaking the code as necessary. One of us (DGG-S) was not blind to the treatment order. He monitored the study and ensured that the dosages of

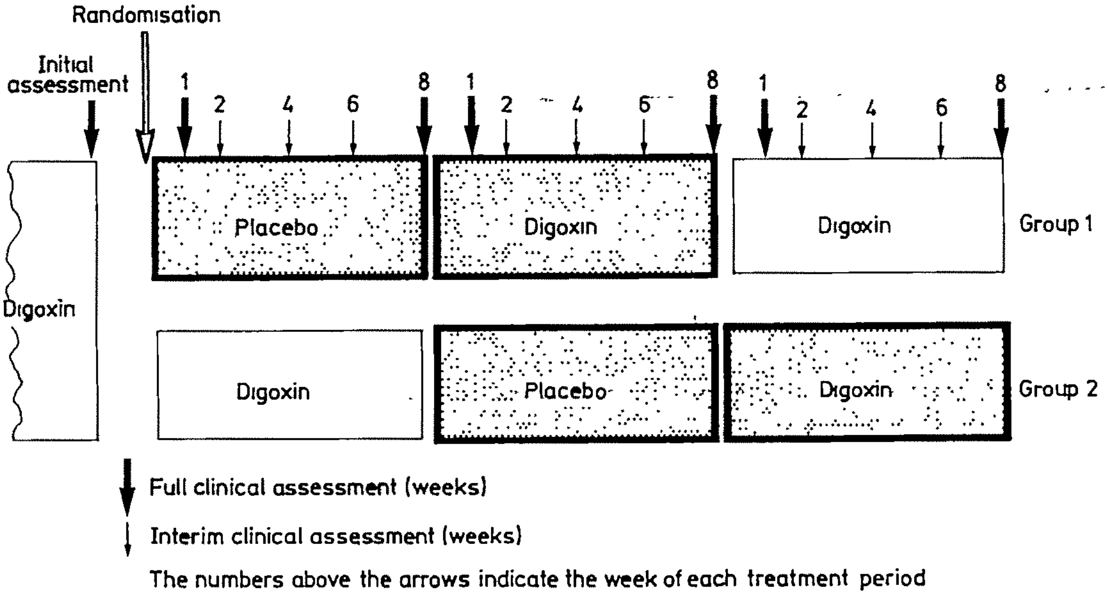

Randomisation
Initial assessment
1
2
4
6
8
Placebo
Digoxin
Digoxin
Group 1
Digoxin
Digoxin
Placebo
Digoxin
Group 2
Full clinical assessment (weeks)
Interim clinical assessment (weeks)
The numbers above the arrows indicate the week of each treatment period

Fig 2 *Treatment randomisation during the study. The stippled boxes show the observation periods that were the subject of statistical analysis. For statistical comparisons the data from the two placebo periods were combined, as were the data from the two digoxin periods immediately after placebo.*

digoxin were adequate to produce the desired plasma concentrations (measured by radioimmunoassay (JGB)).

CLINICAL ASSESSMENT

Each patient's clinical status was assessed on the basis of the presence or absence of the signs and symptoms listed in table 2, and scored as shown there. The total clinical score ranged from 12 (normal) to a maximum of 35 (6–19 for symptoms and 6–16 for signs). Clinical deterioration was defined as a consistent increase in total score of at least two points, one of which had to be attributable to a worsening sign.

HAEMODYNAMIC INVESTIGATIONS

Systolic time intervals were recorded by a Schwarzer C3000 multichannel recorder at a paper speed of 100 mm/s with (*a*) a phonocardiograph to pick up the initial high frequency component of the second heart sound at the point on the chest where the second sound was loudest, (*b*) a pressure transducer held over the right carotid artery, and (*c*) the lead of the conventional electrocardiogram that most clearly showed the onset of the QRS component (usually lead II).

Measurements of systolic time intervals were taken under the same conditions throughout the study, at the same time of day, with patients lying at an angle of 45°, and after they had rested for at least 15 minutes. We calculated the following intervals as the means of ten consecutive beats and corrected for heart rate using the method of Weissler *et al*[13]: the total electromechanical systole (QS_2I), the left ventricular ejection time (LVETI), the pre-ejection period (PEPI) (all corrected for heart rate), and the ratio of uncorrected PEP/LVET.

Echocardiography with simultaneous electrocardiography was performed on a Smith Kline Ekoline 20 ultrasonoscope, with a sound transducer of frequency 2·25 MHz, and printout via a Cambridge recorder at a paper speed of 100 mm/s. Left ventricular M mode recordings were obtained with consistent echoes from the interventricular septum and posterior endocardium at the level of the tips of the mitral valve leaflets. The position of the patient on the couch and of the transducer on the chest wall were recorded on the first occasion, and subsequent measurements were made in the same positions at the same time of day. The left ventricular internal diameter was measured in diastole ($LVID_d$) at the time of the peak of the R wave of the simultaneous electrocardiogram and in systole ($LVID_s$) when the diameter was at a minimum. The dimensions were calculated as the means of six consecutive beats. Fractional shortening and mean velocity of circumferential fibre shortening (VCF) were calculated as follows:

$$\text{Fractional shortening } (\%) = \frac{(LVID_d - LVID_s) \times 100}{LVID_d}$$

$$\text{VCF (circ/s)} = \frac{LVID_d - LVID_s}{LVID_d \times LVET}$$

A trial of exercise tolerance was performed in each patient before randomisation, on a treadmill with simultaneous electrocardiographic recording of resting and peak heart rates. A level of exercise at which the patient became dyspnoeic at or before 10 minutes was determined, and the rate of the treadmill was then reduced to the point at which the patient could just exercise for 10 minutes without dyspnoea. Thus any deterioration in exercise capacity was assessed by either the occurrence of dyspnoea during exercise or the patient's inability to complete the exercise test. Patients taking β adrenoceptor antagonists were excluded from this assessment.

Table 2 *Scoring system for the clinical assessment of signs and symptoms of cardiac failure*

	1 point	*2 points*	*3 points*
Symptoms:			
Orthopnoea	Up to two pillows	More than three pillows	Sleeping upright
Paroxysmal nocturnal dyspnoea	None	Occasional	Every night
Stairs (no of flights)	> 2	One or two	< 1
Distance walked	> 100 yd (90 m)	50–100 yd (45–90 m)	< 50 yd (45 m)
NYHA grade (dyspnoea)	Severe exertion	Moderate exertion	Mild exertion
Palpitation	None	Occasional	Every day
Signs:			
Third heart sound	Absent	Present	
Jugular venous pressure	0–2 cm	2–6 cm	> 6 cm
Peripheral oedema	Absent	To ankles	Above ankles
Tender hepatomegaly	Absent	Present	
Pulmonary oedema	Absent	Basal crackles	Extensive crackles
Heart rhythm	Sinus		Atrial fibrillation

NYHA, New York Heart Association.

PHARMACOLOGICAL MEASUREMENTS

The specific binding of [^{3}H]-digoxin to the membranes of intact erythrocytes, a measure of the number of membrane bound sodium, potassium-adenosine triphosphatase (Na^+, K^+-ATPase; sodium/potassium pump) sites, and the rate of influx of rubidium-86 into intact erythrocytes were measured as previously described.[14,15] Intraerythrocytic sodium concentrations were measured by atomic absorption spectrophotometry after the cells had been washed three times in isotonic magnesium chloride.

STATISTICAL ANALYSIS

Statistical comparisons were made by the following tests where appropriate: χ^2 test; Wilcoxon's rank sum test; Student's paired or unpaired one-tailed or two-tailed *t* tests; one way analysis of variance with Tukey's test for individual differences.

Results

The design of the study (fig 2) allowed us to analyse both the effects of *withdrawing* digoxin (by combin-

both the effects of *withdrawing* digoxin (by combin-

ing the placebo data from groups 1 and 2) and the effects of *reintroducing* digoxin (by analysing the digoxin data immediately after placebo treatment in groups 1 and 2 combined). This is illustrated in fig 2, in which the treatment periods that we analysed are shown in the stippled boxes. There were no statistically significant differences in any of our methods of assessment between groups 1 and 2 during any of the corresponding treatment periods—for example, the measurements made immediately before the introduction of placebo were the same in group 1 as in group 2.

ENTRY ASSESSMENT

Table 3 shows the values at entry of the various measurements we made. There were no differences in any of these measurements when we compared those patients who subsequently deteriorated clinically with those who did not. In addition, there were no differences among the groups in terms of other drug treatments before the study (table 1), although the numbers of patients taking β adrenoceptor

Table 3 *Clinical, haemodynamic, pharmacological, and biochemical measurements at entry into the study (median (range) or mean (SD))*

					Deteriorators			
	Total (n = 44)		*Non-deteriorators (n = 28)*		*Placebo (n = 11)*		*Digoxin (n = 5)*	
Clinical score								
Symptoms	8	(6–12)	8	(6–12)	9	(6–11)	8	(6–8)
Signs	6	(6–12)	6	(6–9)	7	(6–12)	7	(6–9)
Total score	15	(12–24)	14	(12–19)	15	(13–23)	14	(13–17)
Blood pressure (mm Hg):								
Systolic	135	(18)	139	(19)	132	(12)	132	(21)
Diastolic	81	(10)	80	(10)	82	(10)	84	(9)
Exercise heart rates (beats/min):								
Resting	75	(12)	75	(14)	69	(8)	73	(22)
At peak exercise	108	(16)	107	(13)	108	(20)	116	(15)
Cardiothoracic ratio (%)	52	(40–67)	54	(40–61)	53	(44–57)	52	(48–67)
Plasma biochemistry:								
Sodium (mmol/l)	140	(3·1)	140	(3·5)	141	(2·1)	134	(2·0)
Potassium (mmol/l)	4·2	(0·5)	4·2	(0·4)	4·0	(0·4)	4·5	(0·7)
Urea (mmol/l)	7·4	(2·0)	7·3	(2·2)	7·5	(1·4)	7·7	(2·1)
Creatinine (μmol/l)	111	(48)	112	(59)	108	(19)	110	(22)
Erythrocytic measurements:								
[^{3}H]-digoxin binding (pg/0·5 ml cells)	2544	(878)	2460	(685)	2876	(1257)	2168	(746)
Rubidium-86 influx (pmol/l/h)	1·90	(0·47)	1·96	(0·49)	1·87	(0·48)	1·59	(0·22)
Intracellular sodium (mmol/l)	7·1	(1·9)	7·1	(1·6)	7·3	(2·7)	6·8	(1·5)
Systolic time intervals (ms):								
QS_2I	531	(27)	530	(21)	536	(33)	529	(16)
LVETI	392	(27)	394	(21)	387	(33)	403	(32)
PEPI	137	(26)	136	(21)	143	(43)	125	(20)
PEP/LVET	0·394	(0·121)	0·383	(0·087)	0·451	(0·186)	0·539	(0·140)
Echocardiography:	n = 33		n = 21		n = 10		n = 2	
$LVID_d$ (cm)	5·6	(1·3)	5·4	(1·1)	6·1	(1·5)	4·8	(0·1)
$LVID_s$ (cm)	4·1	(1·1)	3·9	(0·9)	4·5	(1·6)	3·2	(0·1)
Fractional shortening (%)	27·6	(7·9)	27·4	(5·4)	26·9	(12·2)	33·7	(2·5)
VCF (circ/s)	0·88	(0·28)	0·94	(0·22)	0·74	(0·36)	1·04	(0·11)

QS_2I, total electromechanical systole corrected for heart rate; LVETI, left ventricular ejection time corrected for heart rate; PEPI, pre-ejection period corrected for heart rate; $LVID_d$ and $LVID_s$, left ventricular internal diameters measured in diastole (d) or systole (s); VCF, velocity of circumferential fibre shortening.

antagonists were too small to detect what may have been a true difference between the groups (9% in placebo deteriorators, 20–25% in the other groups).

CLINICAL DETERIORATION DURING THE STUDY

During the study 28 (64%) of the 44 patients showed no evidence of clinical deterioration on clinical assessment or on exercise testing. Of the other 16, 11 (25% of the total) deteriorated during the placebo period (increases in scores of 2–9 points, median 3), and five (11%) patients deteriorated while taking digoxin (increases in scores of 2–4 points, median 3). Of the 11 who deteriorated while taking placebo, heart failure became worse in nine and two went into atrial fibrillation (both also with worsening heart failure). Of the five who deteriorated while taking digoxin, three developed worsening heart failure and two went into atrial fibrillation, but without heart failure. Among those who deteriorated, four patients had to be withdrawn from the study; of these, two deteriorated while taking placebo (one heart failure, one atrial fibrillation) and two deteriorated while taking digoxin (one heart failure, one atrial fibrillation). Worsening of heart failure while on placebo in those patients who were not withdrawn from the study was treated by increasing doses of diuretics, with a successful outcome in all but two cases, in whom heart failure resolved only on reintroduction of digoxin. In two patients worsening of heart failure in sinus rhythm while on digoxin was successfully treated with increased dosages of diuretics.

Table 4 shows the occurrence of deterioration in terms of the numbers of treatment periods during which deterioration did or did not occur. There were significantly more occasions on which deterioration occurred during placebo periods than during digoxin periods, both when the patients who developed atrial fibrillation are included ($p < 0{\cdot}04$) and when they are not ($p = 0{\cdot}02$).

Table 4 *Clinical deterioration during the study, analysed by treatment period*

	Number of 8 week periods·	
	With deterioration	*Without deterioration*
Digoxin treatment periods	5 (3)	37 (37)
Placebo treatment periods	13 (11)	29 (29)
	$p < 0{\cdot}04$ ($p = 0{\cdot}02$)	

The figures in parentheses are those when patients who developed atrial fibrillation are excluded.

SYSTOLIC TIME INTERVALS

Figure 3 shows the systolic time intervals measured at five different times: (1) immediately before the withdrawal of digoxin; (2 and 3) after placebo treatment for one week and eight weeks respectively; (4 and 5) after the reintroduction of digoxin for one week and eight weeks respectively.

The data were subdivided to compare those who deteriorated during a placebo period with those who did not deteriorate at all. In addition, the systolic time intervals at the time of deterioration are shown for those who deteriorated while they were taking placebo. There were too few data to allow conclusions about the changes in systolic time intervals in patients who deteriorated while taking digoxin.

In those who deteriorated during withdrawal of digoxin there was a significant increase in total electromechanical systole (QS_2I) after withdrawal and a decrease after reintroduction. These changes in QS_2I were attributable to similar changes in the pre-ejection period (PEPI), and there were no significant changes in the left ventricular ejection time (LVETI)

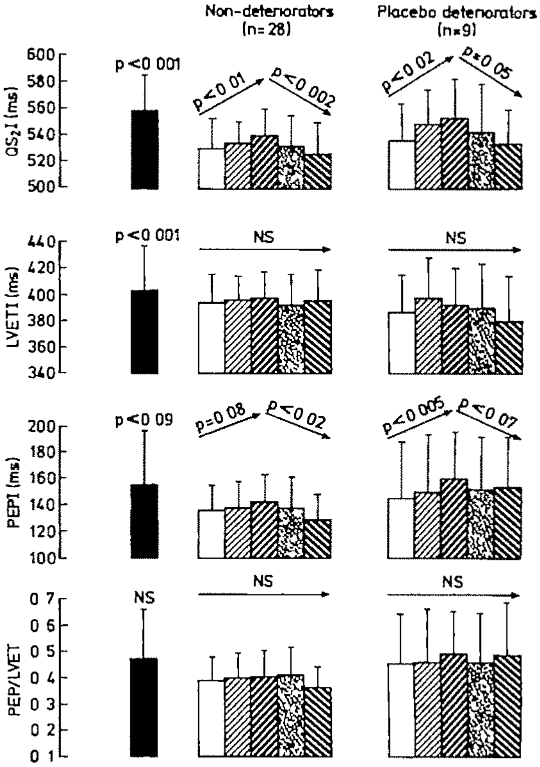


Fig 3 *Systolic time intervals at different times of the study*
■ *At time of deterioration during placebo*
☐ *Immediately before withdrawal of digoxin*
▨ *After placebo treatment for one week*
▨ *After placebo treatment for eight weeks*
▩ *After digoxin reintroduction for one week*
▨ *After digoxin reintroduction for eight weeks*
The same key is used in figs 4 and 5.

or the ratio of PEP:LVET. Similar changes, but of smaller magnitude, were seen in patients who did not deteriorate at any time during the study. In contrast, the systolic time intervals (QS_2I, LVETI, and PEPI) were all significantly higher at the time of deterioration than at entry into the study, and also, in the cases of QS_2I and LVETI, than at the times of reintroduction of digoxin. However, the ratio PEP:LVET did not change during deterioration. Note that the values taken during the eighth week of placebo in those patients who deteriorated relate to patients whose clinical deterioration had, in most cases, been ameliorated by increases in dosages of diuretics.

An analysis of this kind including all those who deteriorated at any time during the study showed exactly the same patterns of change as shown by those who deteriorated while on placebo.

ECHOCARDIOGRAPHY

Figure 4 shows the changes in left ventricular internal diameter sizes during diastole ($LVID_d$) and during systole ($LVID_s$) and the derived measures of ventricular contractility (fractional shortening and mean velocity of circumferential fibre shortening (VCF)) during the study. There were no changes in any of these echocardiographic measurements. In contrast with the systolic time intervals, however, we do not have any echocardiographic measurements in deteriorators at the time of deterioration.

EXERCISE HEART RATES

There were no changes in either resting heart rates just before exercise or peak heart rates during exercise, after either the withdrawal or the reintroduction of digoxin in any of the patients (data not illustrated).

PHARMACOLOGICAL MEASUREMENTS

Figure 5 shows the results of the erythrocytic specific binding of [^{3}H]-digoxin and uptake of rubidium-86. In those who did not deteriorate during digoxin withdrawal there was no change in either [^{3}H]-digoxin binding or uptake of rubidium-86 during the eight weeks after withdrawal. One week after the reintroduction of digoxin, however, both [^{3}H]-digoxin binding and uptake of rubidium-86 fell (consistent with occupation of erythrocytic sodium/potassium pump sites and inhibition of ion transport) and then rose again after eight weeks of continuous treatment (consistent with pharmacological tolerance to the effects of digoxin, as we have described before[11]). In contrast, in those who did deteriorate after digoxin withdrawal this pattern of changes was reversed. After one week of withdrawal there was an increase in both the number of binding sites and the rate of rubidium-86 transport, consistent with rebound from the effects of digoxin, and after eight weeks these had both returned to the values found before withdrawal. After the reintroduction of digoxin there were no changes in either binding or uptake.

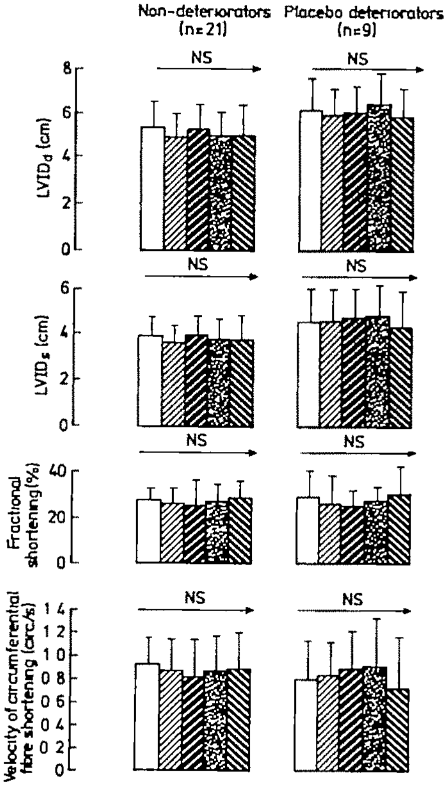


Fig 4 *Echocardiographic $LVID_d$, $LVID_s$, fractional shortening, and VCF at different times of the study. See fig 3 for key.*

Figure 5 shows the changes in intraerythrocytic sodium concentration during the withdrawal and reintroduction of digoxin. In those who did not deteriorate there was no change in intraerythrocytic sodium concentrations after digoxin withdrawal, but a significant increase after its reintroduction, an increase which persisted at eight weeks. In the deteriorators there was both a fall in intraerythrocytic sodium concentrations after the withdrawal of digoxin and an increase after its reintroduction.

Thus a comparison of deteriorators and non-deteriorators showed differences in the patterns of change in all three pharmacological measurements after the withdrawal and reintroduction of digoxin.

Discussion

We know of five previous randomised, double blind,

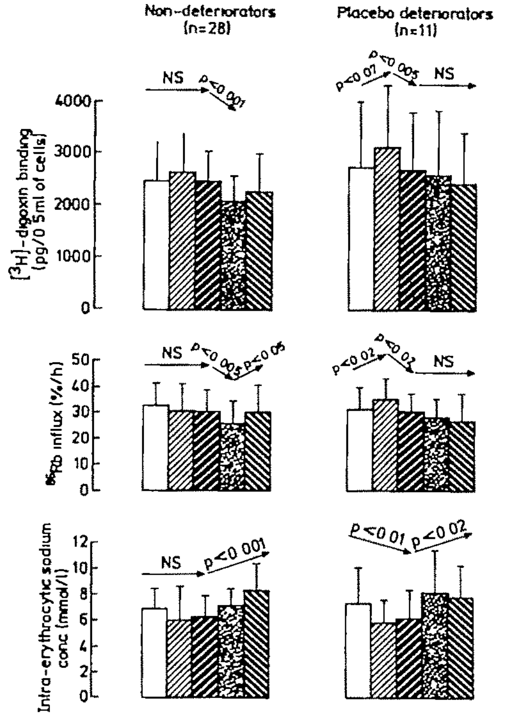


Fig 5 *Erythrocytic [^{3}H]-digoxin binding, uptake of rubidium-86, and intraerythrocytic sodium concentrations at different times of the study. See fig 3 for key.*

placebo controlled, crossover comparisons of digoxin with placebo after long term treatment for heart failure.[7 9 10 16 17] In none of those was there a simultaneous comparison of the changes in the clinical, haemodynamic, and pharmacological effects of digoxin after its withdrawal. Nor was there a systematic comparison of the differences in changes in such effects between those who showed clinical deterioration after withdrawal and those who did not. We therefore compared haemodynamic and pharmacological changes after the withdrawal of digoxin with the clinical consequences of withdrawal, and in particular we compared those patients in whom withdrawal resulted in clinical deterioration with those in whom it did not.

OCCURRENCE OF CLINICAL DETERIORATION DURING THE STUDY

To determine the occurrence of deterioration during the period of study we used a scoring system similar to those previously used by others,[7 10 17] and designed to detect changes in both signs and symptoms. We defined deterioration quite stringently, requiring a consistent increase in total score of at least two points, and a worsening of at least one sign of cardiac failure. In those whom we considered not to have deteriorated clinically (a judgement that was reached before the analysis of the other data), though there were occasional increases of one or two points in the scores relating to symptoms, these were not consistently present during the relevant study period, and required no changes in treatment.

The results show firstly that by these criteria most patients (64%) did not have evidence of clinical deterioration during the study, and secondly that when deterioration occurred it did so in some cases (11%) despite the continuing presence of digoxin. In only 25% of patients did clinical deterioration occur after digoxin withdrawal. Even then we found it possible to control worsening heart failure simply by increasing the dose of diuretics, and in only two patients (5%) did we find that cardiac failure did not resolve until digoxin was reintroduced. In two other patients digoxin was required to control fast atrial fibrillation which occurred during placebo treatment.

Thus although the proportion of patients deteriorating during our study (36%) was similar to that previously found by others,[2 3] in only 25% of cases was deterioration directly attributable to a loss of the beneficial effect of digoxin rather than to deterioration caused by the natural course of cardiac failure, and in only four cases (9%) was reintroduction of digoxin necessary.

Two of the four patients who developed atrial fibrillation during the study did so while taking digoxin (plasma digoxin concentrations 1·6 and 1·3 ng/ml). This is consistent with the widespread belief that digoxin may not be useful in preventing atrial fibrillation (for example in paroxysmal atrial fibrillation).

HAEMODYNAMIC CHANGES AFTER DIGOXIN WITHDRAWAL AND REINTRODUCTION

The changes in systolic time intervals at the time of onset of clinical deterioration while on placebo (fig 3, left hand panel) are consistent both with worsening of cardiac failure because of reduced left ventricular contractility (as assessed by a prolongation of the left ventricular ejection time) and with the loss of the usual effects of digoxin on cardiac conduction (reflected in a lengthening of total electromechanical systole) not entirely attributable to the lengthening of the ventricular ejection time. One would have expected the ratio of pre-ejection period (PEP) to the left ventricular ejection time (LVET) to have decreased with worsening heart failure because of the lengthening of the LVET, but because of the concomitant loss of the effect of digoxin on the PEP, albeit a small effect, there was no significant change in PEP:LVET. This is consistent with our previous observations that although total electromechanical systole and LVETI shorten significantly when heart failure responds to treatment with digoxin, the ratio of PEP:LVET does not alter.[14]

By the end of the eighth week of placebo treatment in these patients, who had deteriorated after withdrawal of digoxin, there was clinical improvement in cardiac function caused by the administration of increased dosages of diuretics, and in consequence the LVETI once again shortened (fig 3, right hand panel). This is also consistent with the lack of overall change in echocardiographic measurements over the same period of time. None the less, at that time there was still significant lengthening of the QS_2I and PEPI, indicative of the continuing absence of the effects of digoxin. In the patients who had not deteriorated (fig 3, middle panel) there was no change in myocardial contractility, as assessed by the LVETI and echocardiographic measurements, but there was none the less evidence of a loss of the effects of digoxin, as assessed by increases in QS_2I and PEPI. These changes were smaller than the changes seen in the patients who deteriorated while on placebo, but nevertheless they suggest that digoxin was exerting a pharmacodynamic effect on the heart that was not contributing to the control of heart failure in these patients, and which could therefore be lost after withdrawal without consequent deterioration of the patients' clinical state.

After the reintroduction of digoxin the systolic time intervals QS_2I and PEPI shortened in both groups, showing that the heart was still responsive to the electrophysiological effects of digoxin. In contrast, there was no overall change in LVETI or PEP/LVET in either group. This suggests that in patients in whom diuretic treatment has been successful in relieving the signs and symptoms of heart failure, digitalis has little to offer in the way of additional positive inotropic support. In patients who deteriorated, the fall in LVETI from the time of deterioration to the time of reintroduction of digoxin may be attributable to improvement in left ventricular function secondary to increases in diuretic dosages.

CHANGES IN EXERCISE TESTING DURING WITHDRAWAL

We were unable to carry out exercise testing at every visit, and therefore could not detect any changes in exercise capacity or peak heart rate during exercise at times of deterioration. By the eighth week of placebo treatment the exercise responses were unchanged, even in those who had previously deteriorated clinically, presumably because of the increases in diuretic dosages. This observation is consistent with the finding of others that digoxin does not improve exercise tolerance in patients in whom diuretics have been used to produce a stable body weight.[18]

CHANGES IN PHARMACOLOGICAL MEASUREMENTS DURING WITHDRAWAL AND REINTRODUCTION OF DIGOXIN

There are clearly differences in the patterns of change during withdrawal and reintroduction of digoxin when those who deteriorated are compared with those who did not. Two features of these patterns are particularly noteworthy.

Firstly, in those who deteriorated, but not in those who did not, withdrawal of digoxin was associated with a rebound in both [^{3}H]-digoxin binding and uptake of rubidium-86, both of which rose at one week after withdrawal and then returned to prewithdrawal values after eight weeks. This suggests that in those who deteriorated the effects of digoxin in occupying sodium/potassium pump sites, and thus in inhibiting transport, were lost during withdrawal. This was accompanied at one week by a fall in intraerythrocytic sodium concentration. If that also happened in the heart it could have been responsible for the loss of therapeutic effect seen in these patients, by causing secondary changes in calcium disposition in the opposite direction from the changes that have been postulated to occur as part of the positive inotropic action of digitalis.[19]

Secondly, after the reintroduction of digoxin in the non-deteriorators, but not in the deteriorators, there was a fall in binding and uptake and at eight weeks a return to the values found before reintroduction. This shows that the sodium/potassium pump sites in the erythrocytes of these patients were still capable of both responding to the pharmacological effects of digoxin and of adapting to those effects, as we have previously shown.[11]

It is not clear to us why rebound after withdrawal did not occur in those who did not deteriorate nor why there was no evidence of a pharmacological effect on the erythrocytes after reintroduction in those who did deteriorate. It may be that there is a difference in the time course of effects in the two groups, and that we have failed to detect changes because we took samples only at one and eight weeks. Alternatively, it may be that other mechanisms participate in the control of the numbers and activity of Na/K-ATPase sites on the erythrocyte membrane, and that these differ in deteriorators and nondeteriorators. For example, an endogenous inhibitor of the sodium/potassium pump, with a different rate of turnover in the two groups, could have produced differential results. The fact that the intraerythrocytic sodium concentrations showed different patterns of change from the two other pharmacological measurements suggests that other factors may have played a part.

PREDICTION OF DETERIORATION BEFORE WITHDRAWAL

It would clearly be of value to have a measurement or observation in patients on long term digoxin treatment that would help to predict whether or not deterioration might be expected after digoxin withdrawal. However, none of the measurements we made at the time of entering patients into the study proved of value in discriminating between those patients who subsequently deteriorated and those who did not (table 3). This finding is consistent with the findings of other workers who were unable to relate the outcome of withdrawal to any one of several measures, including age, sex, New York Heart Association class, the use of diuretics, the previous duration of digoxin treatment, the cause of the heart disease, and cardiac rhythm.[7 10] In one study the presence of a third heart sound was found to be a good predictor of deterioration,[16] presumably since it reflects relatively poor left ventricular contraction. None of our patients had a third heart sound at entry to the study and we cannot therefore make any conclusions about that. Patients with plasma digoxin concentrations below 0·8 ng/ml are very unlikely to deteriorate after digoxin withdrawal,[4 20] but this could not have contributed to our results since we studied patients with plasma digoxin concentrations $\geqslant$0·8 ng/ml at entry to the study, and during digoxin treatment periods used dosages of digoxin which kept the plasma concentrations above 0·8 ng/ml.

It is clear from the results of this and other studies that digoxin continues to exert a beneficial effect in some patients with heart failure in sinus rhythm.

There are, however, no clear-cut criteria to predict which patients will deteriorate after digoxin withdrawal. Nevertheless, it is possible to formulate guidelines for the use of digoxin in the long term management of heart failure in sinus rhythm:

(*a*) If a patient is in a stable condition and has a plasma digoxin concentration below 0·8 ng/ml digoxin withdrawal is very likely to be safe. It has been suggested by others that this applies to patients not only in sinus rhythm but also in atrial fibrillation.[4 20]

(*b*) If a patient is in a stable condition, has a plasma digoxin concentration $\geqslant$0·8 ng/ml, and is not at great risk of toxicity, digoxin withdrawal is probably not worth while, because there is a 25% risk of deterioration.

(*c*) If, however, there is an increased risk of digitalis toxicity (for example in a patient with deteriorating renal function, or in one who has difficulty in maintaining potassium balance) then careful withdrawal may be worth attempting.

(*d*) In a few patients (for example those with a third heart sound) it may be better to continue treatment, even when there is an increased risk of digitalis toxicity. In that case, however, monitoring of treatment should be increased to reduce the risk of toxicity.

Throughout this discussion we have assumed that digoxin treatment was thought to be appropriate in the first place, either alone or in addition to diuretics, vasodilators, or angiotensin converting enzyme inhibitors. As alternative forms of treatment become available the role of digitalis in the long term management of cardiac failure will undoubtedly evolve further.

SEP and JKA acknowledge the support of the Wellcome Trust. Additional financial support was given by the Oxfordshire Regional Health Authority. The Wellcome Foundation Ltd kindly supplied dummy tablets to match Lanoxin.

References

1 Withering W. *An account of the foxglove and some of its medical uses: with practical remarks on dropsy and other diseases*. Paternoster-Row, London: G G J and J Robinson, 1785.

2 Aronson JK. Cardiac glycosides and drugs used in dysrhythmias. In: Dukes MNG, ed. *Side effects of drugs, annual 4*. Amsterdam: Excerpta Medica, 1980:122–6.

3 Fleg JL, Lakatta EG. How useful is digitalis in patients with congestive heart failure and sinus rhythm? *Int J Cardiol* 1984;6:295–305.

4 Johnston GD, McDevitt DG. Is maintenance digoxin necessary in patients with sinus rhythm? *Lancet* 1979;i:567–70.

5 Sommers DeK, Reitz CJ, Koch K, Avenant JC. Digoxin withdrawal in patients with sinus rhythm. *S Afr Med J* 1981;60:239–40.

6 Gheorghiade M, Beller G. Effects of discontinuing maintenance digoxin therapy in patients with ischemic heart disease and congestive heart failure in sinus rhythm. *Am J Cardiol* 1983;51:1243–50.

7 Dobbs SM, Kenyon WI, Dobbs RJ. Maintenance digoxin after an episode of heart failure: placebo-controlled trial in outpatients. *Br Med J* 1977;i:749–52.

8 Griffiths BE, Penny WJ, Lewis MJ, Henderson AH. Maintenance of the inotropic effect of digoxin on long-term treatment. *Br Med J* 1982;284:1819–22.

9 Fleg JL, Gottlieb SH, Lakatta EG. Is digoxin really important in treatment of compensated heart failure? A placebo-controlled crossover study in patients with sinus rhythm. *Am J Med* 1982;73:244–50.

10 Taggart AJ, Johnston GD, McDevitt DG. Digoxin

withdrawal after cardiac failure in patients with sinus rhythm. *J Cardiovasc Pharmacol* 1983;**5**:229–34.

11 Aronson JK, Ford AR, Grahame-Smith DG. Techniques for studying the pharmacodynamic effects of cardiac glycosides on patients' own erythrocytes during glycoside therapy. *Klin Wochenschr* 1981; **59**:1323–32.

12 Cumberbatch M, Zareian K, Davidson C, Morgan DB, Swaminathan R. The early and late effects of digoxin treatment on the sodium transport, sodium content and Na^+K^+-ATPase of erythrocytes. *Br J Clin Pharmacol* 1981;**11**:565–70.

13 Weissler AM, Lewis RP, Leighton RF. The systolic time intervals as a measure of left ventricular performance in man. In: *Progress in cardiology*. Philadelphia: Lea and Febiger, 1972;vol 1:155–83.

14 Ford AR, Aronson JK, Grahame-Smith DG, Carver JG. Changes in cardiac glycoside receptor sites, ^{86}rubidium uptake and intracellular sodium concentrations in the erythrocytes of patients receiving digoxin during the early phases of treatment of cardiac failure in regular rhythm and of atrial fibrillation. *Br J Clin Pharmacol* 1979;**8**:125–34.

15 Aronson JK, Grahame-Smith DG, Hallis KF, Hibble A, Wigley F. Monitoring digoxin therapy. I. Plasma concentrations and an in vitro assay of tissue response. *Br J Clin Pharmacol* 1977;**4**:213–21.

16 Lee DC-S, Johnson RA, Bingham JB, *et al.* Heart failure in outpatients. A randomized trial of digoxin versus placebo. *N Engl J Med* 1982;**306**:699–705.

17 Boman K. Digoxin and the geriatric in-patient. A randomized trial of digoxin versus placebo. *Acta Med Scand* 1983;**214**:353–60.

18 McHaffie D, Purcell H, Mitchell-Heggs P, Guz A. The clinical value of digoxin in patients with heart failure and sinus rhythm. *Q J Med* 1978;**NS48**:401–19.

19 Noble D. Mechanism of action of therapeutic levels of cardiac glycosides. *Cardiovasc Res* 1980;**14**:495–514.

20 Liverpool Therapeutics Group. Use of digitalis in general practice. *Br Med J* 1978;**ii**:673–5.

Br Heart J 1989;61:540–5

Anomalous subaortic position of the brachiocephalic (innominate) vein: a review of published reports and report of three new cases

LEON M GERLIS, SIEW YEN HO

From the Department of Paediatrics, National Heart and Lung Institute, London

SUMMARY Anomalous courses of the left innominate vein have rarely been described in anatomical specimens. Investigative techniques such as angiography and echocardiography have brought to light more instances of this anomaly. Three more cases identified by anatomical study are described. Earlier cases were reviewed to assess the type of associated cardiac malformations. Clinically, the abnormality is regarded as benign. When it is recognised during investigation it should alert the clinician to the possibility of associated malformations. Features commonly seen in tetralogy of Fallot—right aortic arch, ventricular septal defect, and right ventricular outflow obstruction—were common in patients with anomalous subaortic innominate veins.

The left brachiocephalic (or innominate) vein extends from the junction of the left internal jugular and left subclavian veins to the junction of the right brachiocephalic (or innominate) vein and the (right) superior caval vein. The normal course is obliquely downwards and to the right, passing in front of the left subclavian, left common carotid, and brachiocephalic arteries, beneath the aortic arch.[1] Very rarely, this vein (or its analogue) follows an anomalous course, passing from left to right below the arch of the aorta, to enter the (right) superior caval vein below the orifice of the azygos vein. Kershner first described this anomaly a hundred years ago,[2] and we are aware of at least another 21 cases (table). We report three further cases.

Although the malformation in itself seems to be of no functional importance, we assessed its importance in terms of associated conditions and its possible relevance to subsequent operations.

Case reports

CASE 1

This girl died when she was 5 years 11 months old after cerebral ischaemia after attempted surgical correction of tetralogy of Fallot. Postmortem examination of the heart showed usual (solitus) atrial arrangement with concordant atrioventricular and ventriculoarterial connections, infundibular and valvar pulmonary stenosis, subaortic ventricular septal defect, and several large aortopulmonary anastomoses. There was a right sided aortic arch. The site of the arterial duct was not apparent. The large left brachiocephalic vein passed behind the ascending aorta and below the aortic arch before entering the superior caval vein (vena cava), below the level of the azygos vein and just above its junction with the right atrium (fig 1).

CASE 2

This male infant died of complex cardiac malformation at one day. There was the usual (solitus) atrial arrangement with concordant atrioventricular connection and double outlet right ventricle with a dextroposed aortic orifice overriding a perimembranous ventricular septal defect. There appeared to be an ectopic portion of atrioventricular valve, complete with leaflet tissue, tendinous cords, and papillary muscles, situated between the trabecular and infundibular components of the right ventricle. The unguarded pulmonary artery orifice showed no trace of arterial valve leaflets. The arterial duct was short and widely patent. The aortic arch was left sided and had normal branches. The left internal jugular vein continued into a descending vein, which passed under the aortic arch from left to right, anterior to the arterial duct and between the arch and the pulmonary trunk. It then ran behind the ascending aorta to enter the lower portion of the superior

Requests for reprints to Dr Leon M Gerlis, Department of Paediatrics, National Heart and Lung Institute, Dovehouse Street, London SW3 6LY

Accepted for publication 20 January 1989

Table *Reported cases of subaortic left brachiocephalic vein*

Case	*Authors*	*Year*	*Reference No*	*Age*	*Sex*	*Diagnosis*	*Relation to arterial duct*	*Aortic arch*	*Other cardiovascular malformations*
1	Kerschner	1888	2	? (child)	?	Necropsy	?	L	None
2	Daser	1902	6	68 yr	M	Necropsy	Anterior	L	None
3	Ghon	1908	7	4½ mnth	F	Necropsy	Posterior	R	Absent L 4th arch, isolated L subclavian artery
4	Nützel	1914	8	74 yr	M	Necropsy	?	L	Right superior pulmonary vein to superior caval vein
5	Martin	1931	9	17 yr	M	Necropsy	Anterior	R	Fallot
6	Walter	1931	10	19 yr	M	Necropsy	Anterior	L	Subthyroid venous anastomosis
7	Adachi	1933	11	20 yr	M	Necropsy	Anterior	L	None
8	Adachi	1933	11	41 yr	M	Necropsy	Posterior	L	None
9	Friedman	1945	12	66 yr	M	Necropsy	Anterior	L	L jugular vein anomaly
10	Roberts *et al*	1951	1	7 yr	F	Angio	Subpulmon art	L	None
11	Sherman	1963	4	?	?	Necropsy	Anterior	L	Pulmonary atresia VSD
12	Sherman	1963	4	?	?	Necropsy	Anterior	L	Pulmonary atresia VSD
13	Yoshida *et al*	1975	13	68 yr	M	Necropsy	Anterior	L	None
14	Kitamura *et al*	1981	14	69 yr	M	Necropsy	Anterior	L	None
15	Cloez *et al*	1982	15	1½ yr	M	Echo and angio	?	L	Fallot
16	Smallhorn *et al*	1985	5	?	?	Echo	?	R	Right outflow tract anomalies "frequent". Intra cardiac anomalies in six (? VSDs). Central pulmonary arteries absent in one
17	Smallhorn *et al*	1985	5	?	?	Echo	?	R	
18	Smallhorn *et al*	1985	5	?	?	Echo	?	R	
19	Smallhorn *et al*	1985	5	?	?	Echo	?	R	
20	Smallhorn *et al*	1985	5	?	?	Echo	?	R	
21	Smallhorn *et al*	1985	5	?	?	Echo	?	R	
22	Smallhorn *et al*	1985	5	?	?	Echo	?	L	
23	Gerlis *et al*	1988	—	5 yr 11 mnth	F	Necropsy	No duct	R	Fallot
24	Gerlis *et al*	1988	—	1 day	M	Necropsy	Anterior	L	Complex
25	Gerlis *et al*	1988	—	7 wk	F	Necropsy	No duct	R	Common arterial trunk

Angio, angiography; echo, echocardiography; subpulmon art, subpulmonary artery; VSD, ventricular septal defect.

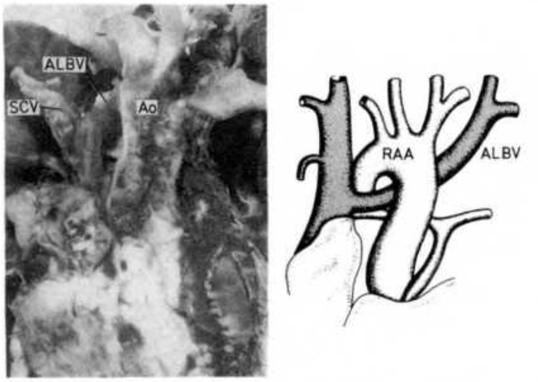


Fig 1 *Photograph and diagram of case 1 showing the anomalous left brachiocephalic vein (ALBV) running behind the ascending aorta (Ao) and below the right aortic arch (RAA) before entering the superior caval vein (SCV).*

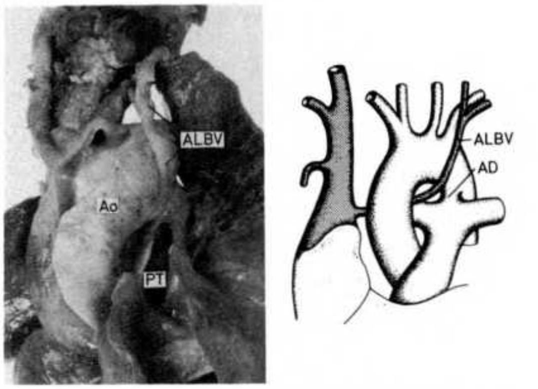


Fig 2 *Photograph and diagram of case 2 showing the anomalous left brachiocephalic vein (ALBV) passing below the aorta (Ao). AD, arterial duct; PT, pulmonary trunk.*

caval vein between the entry of the azygos vein and the junction with the right atrium. Because the specimen was damaged it was impossible to ascertain the connection between this anomalous vein and the left subclavian vein. There was, however, no evidence of any other route of venous drainage from the left arm (fig 2).

CASE 3

This seven week old female infant died after attempted surgical correction of a common arterial trunk. There was the usual atrial arrangement with concordant atrioventricular connection and a subtruncal ventricular septal defect with an overriding quadricuspid truncal valve. The pulmonary arteries originally had separate orifices from the posterior aspect of the common arterial trunk. The aortic arch was right sided and its branches were a mirror image of the normal arrangement. No arterial duct or ligament was present.

The left sided brachiocephalic vein descended to the left of the ascending aorta and then passed behind it to the right side, below the aortic arch, to open into the left medial aspect of the superior caval vein between the entry of the azygos vein and the junction with the right atrium (fig 3).

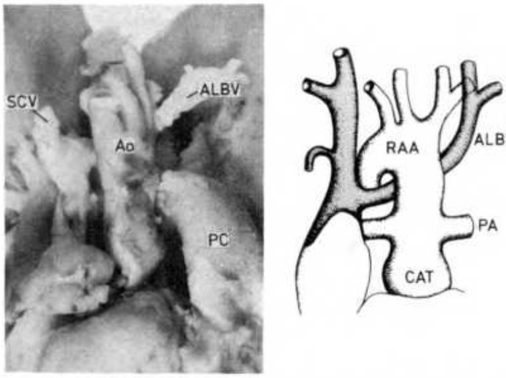


Fig 3 *Photograph and diagram of case 3 showing the anomalous left brachiocephalic vein (ALBV) passing below the right aortic arch (RAA) before entering the superior caval vein (SCV). The photograph shows the vessels after surgical correction of the common arterial trunk (CAT), with the insertion of a pulmonary conduit (PC). The diagram shows the original state before operation. Ao, aorta; PA, pulmonary artery.*

REVIEW OF PUBLISHED REPORTS

The true incidence of the anomaly is difficult to assess. The veins are rarely studied in detail at necropsy. Careless neck incisions, removal of the sternum, or opening of the pericardium may cause bleeding from the veins, which then collapse and become very difficult to see. Removal of the heart often damages or destroys the veins. Angiocardiography does not usually call for visualisation of the right brachiocephalic vein. Increased routine use of suprasternal echocardiography, however, should readily reveal the anomaly if such a possibility is recognised.

A detailed angiographic study of the brachiocephalic veins of over 1500 people showed only one example of a subaortic vein,[1] while another angiographic study of the superior caval veins in 510 patients with congenital heart disease showed no such anomalies.[3] Sherman found two examples among 503 specimens of congenitally malformed hearts[4] and we have encountered three cases out of approximately 2000 congenitally malformed hearts in the combined collections of the Brompton and Killingbeck Hospitals. These combined figures give an incidence of six cases out of about 2500 necropsy cases with congenital heart disease, or approximately one in 500. Smallhorn *et al* found seven cases echocardiographically but the total number of patients examined in the series is not stated.[5]

The incidence in individuals without cardiac malformation is presumably very much lower. In a personal necropsy series, LMG found no subaortic brachiocephalic veins in approximately 5000 individuals without malformed hearts.

In none of the reported cases has it been suggested that the venous anomaly had any adverse physiological or clinical effect. Therefore the age at death or diagnosis was relevant only to associated or unassociated conditions. The ages ranged from one day to 74 years (table). In those cases with congenital heart disease, the mean known age was approximately three years (excluding a 74 year old man with an anomalous connection of the right upper pulmonary vein). In cases with normally formed hearts, the mean age at death was 53 years, supporting the view that the abnormality is clinically benign.

The sex of 15 of the 25 cases was known. Males outnumbered females by 11 to 4. Those cases with congenital heart malformation showed no significant sex difference but all eight cases with normally formed hearts were male.

Features common to tetralogy of Fallot were present in most of the 14 cases with major cardiac malformations. Thus a ventricular septal defect was reported in eight cases and may have been present in another six reported by Smallhorn *et al* in which intracardiac malformations of unspecified types were found by echocardiography.[5] A right sided aortic arch was noted in ten cases and tetralogy of Fallot, pulmonary stenosis, pulmonary atresia, or unspecified abnormalities of the right ventricular outflow tract were present in 11 of the 14. Other malformations were: one example of double outlet right ventricle, one common arterial trunk, and an anomalous isolated subclavian artery arising from an arterial duct (see table). There were minor vascular anomalies in three additional cases in which the heart itself was normal. A 74 year old man had anomalous drainage of the right superior pulmonary vein into the superior caval vein[8]; a 19 year old man had a small subthyroid transverse venous anastomosis,[10] and a man of 66 had minor abnormalities of the jugular vein.[12] There were no instances of associated noncardiovascular malformations.

Three distinct anatomical varieties of the malformation can be recognised according to the relation of the anomalous vein with the arterial duct or ligament (fig 4). The presence and position of this structure

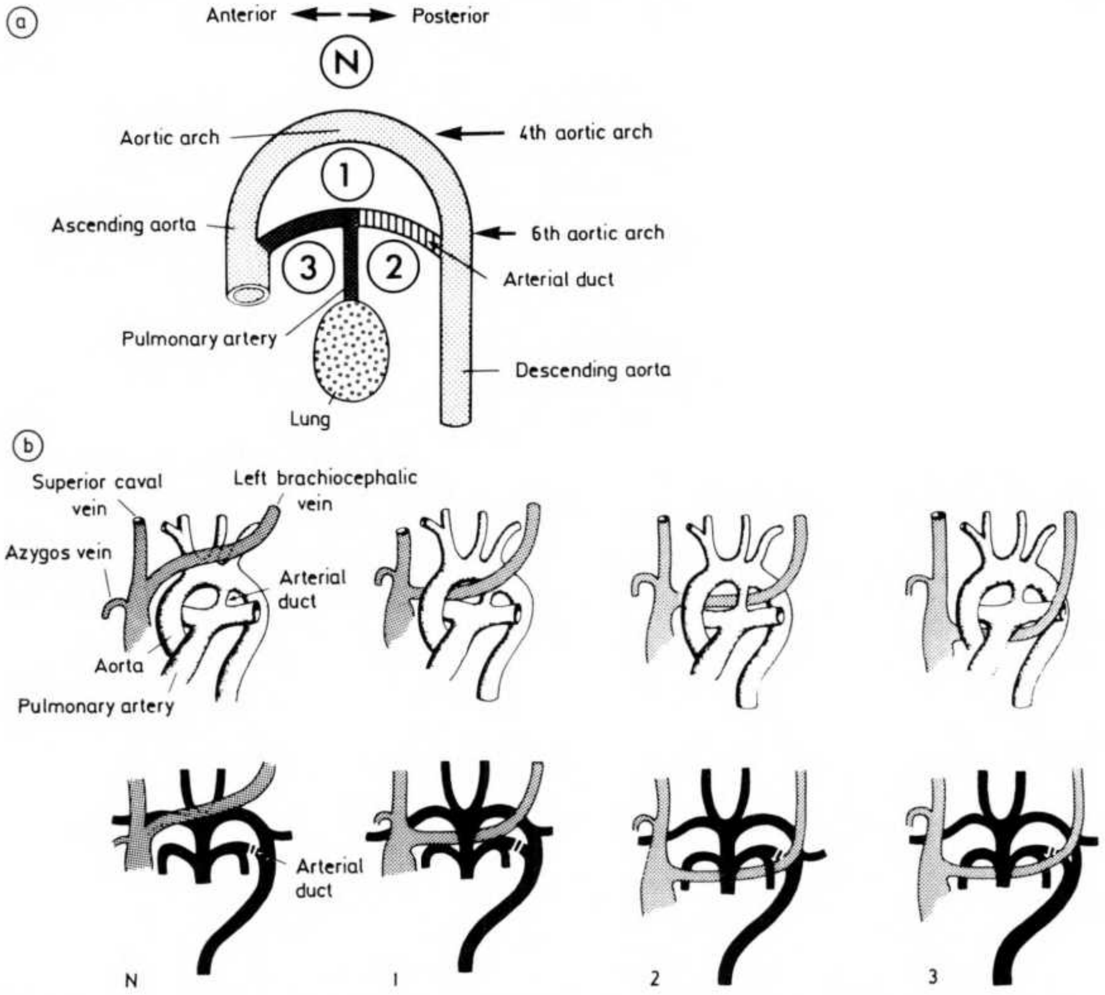


Fig 4 *(a) Diagram showing the positions of the normal (N) and the three variants of the anomalous left brachiocephalic vein (1, 2, 3) in relation to the 4th and 6th left aortic arches as seen from the left side. (b) Diagrams of the normal and abnormal variant venous pathways as seen from the front, with accompanying embryological diagrams.*

was specified or illustrated in 13 cases. In ten, the vein passed anteriorly to the arterial duct or ligament to lie between the underside of the aortic arch and the pulmonary arteries. In two cases, the vein passed posteriorly to the arterial duct or ligament, while in the remaining case it passed below the left pulmonary artery.[1] Three further cases have been described in which the left brachiocephalic vein passed behind one or more of the main aortic branches but was normally related to the aortic arch.[4 5 8 10 12 16] This condition is distinct from the anomalous venous pathway that is the subject of this review.

Discussion

During normal development, the primordia of the systemic veins first appear as paired anterior and posterior cardinal veins that unite on each side to form a common cardinal vein (or cuvierian duct) that opens into the primitive sinus venosus. The anterior cardinal veins extend headwards to the junctions of the internal jugular veins and subclavian veins on each side, but, during subsequent development, most of the left anterior cardinal vein disappears. The venous drainage from the left side of the head and neck and the left arm is then directed into the right anterior cardinal vein by the development of a new transverse anastomotic channel that becomes the left brachiocephalic (or innominate) vein. The short part of the right anterior cardinal vein that lies distal to the opening of the left brachiocephalic vein is designated as the right brachiocephalic vein, while the portion that lies below, together with the right common cardinal vein, becomes the superior caval vein. The orifice of the (right) azygos vein represents the site of entry of the right posterior cardinal vein and marks the junction of the anterior cardinal and common cardinal venous components of the superior caval vein. On the left side the common cardinal vein becomes the coronary sinus, the adjacent portion of the anterior cardinal vein becomes the oblique vein of Marshal, and the posterior cardinal vein becomes the great cardiac vein (fig 5).

Phylogenetically, this venous arrangement is a late development. It is present only in primates and some of the other mammals, with no forerunner in other vertebrate orders.[17] Persistence of bilateral superior caval veins is a common feature in cases of cardiac malformation and in 39%[18] to 43%[3] of these there is no transverse communicating vein; the left sided venous return enters directly into an atrium.

If the lower portion of the left anterior cardinal vein atrophies while the usual transverse anastomosis fails to develop, survival depends on the opening up of an alternative anastomotic pathway within the capillary plexus of that region. This seems to be a possible explanation of the anomalous subaortic position of communicating vein presently described.

The subaortic vein enters the superior caval vein below the insertion of the azygos vein and it thus connects the left anterior cardinal venous component to the right common cardinal venous component. Normally, the left brachiocephalic vein enters the superior caval vein above the insertion of the azygos vein and the connection is between the left and the right anterior cardinal components. The anomalous vein, therefore, is embryologically distinct from the normal left brachiocephalic vein as well as having a different spatial pathway and different anatomical relations. In consequence, the question of terminology could be debated at length. But, because the ultimate connections at either end are identical, it seems reasonable to refer to the structure as an anomalous brachiocephalic vein.

Although not of clinical importance, its recognition during clinical investigation raises the possibility of an association with other malformations, especially right aortic arch, ventricular septal defects, and right ventricular outflow obstruction. Care must be taken not to confuse the structure with other arteries or veins—notably, the central pulmonary arteries in the presence of the pulmonary atresia or a venous confluence in anomalous pulmonary venous connection.[5] From the surgical viewpoint, the anomalous brachiocephalic vein may hinder access to the arterial duct during ductal ligation, or obscure the field in the construction of a subclavian to pulmonary shunt. Dissection in the region of the duct must be performed carefully to avoid damaging a subaortic vein.

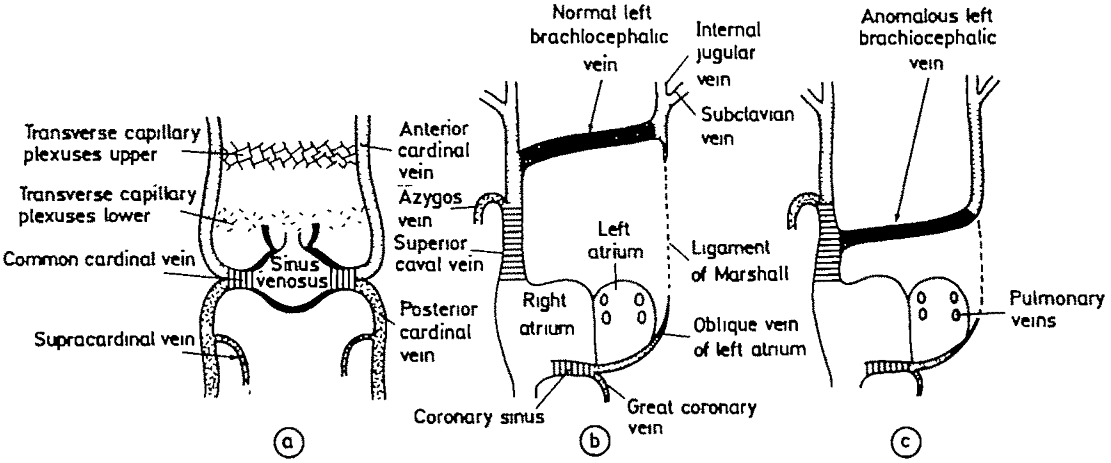


Fig 5 *Diagrams showing embryological derivations of the normal and anomalous left brachiocephalic veins. (a) Early embryological patterns. (b) Normal definitive pattern showing the left brachiocephalic vein entering the right anterior cardinal vein component (above the azygos vein). (c) Abnormal definitive pattern showing the left brachiocephalic vein entering the right common cardinal vein component (below the azygos vein).*

We thank Dr Wilfred Nikolaizik for his valuable assistance in translating some of the references.

This study was supported, in part, by the British Heart Foundation.

References

1 Roberts JR, Dotter CT, Steinberg I. Superior vena cava and innominate veins: angiographic study. *Am J Roent* 1951;**66**:341–52.

2 Kershner L. Zur Morphologie der Vena Cava Inferior. *Anat Anz* 1888;**3**:808–23.

3 Buirsky G, Jordan SC, Joffe HS, Wilde P. Superior vena caval abnormalities: their occurrence rate, associated cardiac abnormalities and angiographic classification in a paediatric population with congenital heart disease. *Clin Radiol* 1986;**37**:131–8.

4 Sherman FE. *An atlas of congenital heart disease.* London: Henry Kimpton, 1963.

5 Smallhorn JF, Zielinsky P, Freedom RM, Rowe RD. Abnormal position of the brachiocephalic vein. *Am J Cardiol* 1985;**55**:234–6.

6 Daser P. Ueber eine seltene Lage-Anomalie der vena anomyma sinistra. *Anat Anz* 1902;**20**:553–5.

7 Ghon A. Ueber eine seltene Entwicklungsstorung des Gefasssystems. *Zbl Path* 1908;**19**:242–7.

8 Nutzel H. Beitrag zur Kenntnis der Missbildungen in Bereiche der oberen Holvene. *Frankf Z Path* 1914;**15**:1–19.

9 Martin CP. A case of congenital abnormality of the heart with apparently an unusual abnormality of the great vessels. *J Anat* 1931;**65**:395–8.

10 Walter L. Uber eine seltene Lageanomalie di vena anomyma sinistra webst Betrachtungen uber anomalien and Asymmetrien des Venensystems in Bereich des Kopfes und Halses. *Z Anat* 1931;**95**: 769–805.

11 Adachi B. *Das Venensystem der Japaner. Anatomie der Japaner II.* Tokyo: Kenkyusha, 1933:83–7.

12 Friedman SM. Report of two unusual venous abnormalities (left postrenal inferior vena cava; post-aortic left innominate vein). *Anat Rec* 1945;**92**:71–6.

13 Yoshida Y, Fukuyama U. A case of the left brachiocephalic vein passing behind the ascending aorta. *Chiba Igaku* 1975;**51**:157–9.

14 Kitamura S, Sakai A, Nishiguchi J. A case of the left innominate vein passing behind the ascending aorta. *Anat Rec* 1981;**201**:567–72.

15 Cloez JL, Ravault F, Marçon F, Pernot C. Tronc veineux innominé en position sous-aortique. Intérêt de l'echocardiographie de contraste par voie suprasteinale. *Arch Mal Coeur* 1982;**75**:939–43.

16 Jakubczik I, Ziegler H. Seltene Anomalein der Grossen intrathoracalen Blut und lymphgefasssstamme. *Anat Anz* 1963;**112**:257–68.

17 Barnett CH, Harrison RJ, Tomlinson JDW. Variations in the venous systems of mammals. *Biol Rev* 1958;**33**:442–78.

18 Winter FS. Persistent left superior vena cava. Survey of world literature and report of thirty additional cases. *Angiology* 1954;**5**:90–132.

Br Heart J 1989;61:546–7

Case reports

Injury to a saphenous vein graft during removal of a temporary epicardial pacing wire electrode

COLIN PRICE, DANIEL J M KEENAN

From the Department of Cardiothoracic Surgery, Manchester Royal Infirmary, Manchester

SUMMARY Removal of a temporary atrial epicardial pacemaker electrode damaged a saphenous vein graft. A new blood clot was removed from the damaged graft. The hole was successfully repaired with a polypropylene suture.

Pacing wires should be carefully sited and should be removed only when facilities for urgent operation are available.

Case report

A 64 year old man with unstable angina underwent urgent saphenous vein aortocoronary bypass grafting. Sequential atrioventricular pacing by temporary epicardial pacemaker electrodes was used to facilitate weaning from cardiopulmonary bypass but the operation was otherwise straightforward. His postoperative course was similarly uncomplicated until the removal of the pacing wires on the seventh day.

Both atrial electrodes were removed easily by gentle traction but he immediately felt unwell and was found to be hypotensive with a profound bradycardia. Fortunately, his ventricular wires were still in place and pacing was started, with initial recovery. Over the next two hours his blood pressure fell and an echocardiogram confirmed the presence of a haemopericardium.

He was transferred to the operating theatre and underwent urgent re-exploration. The right atrium was compressed by a new blood clot (150 ml) originating from a tear in the saphenous vein graft to the right coronary artery. The haematoma was evacuated and, after systemic heparinisation, the graft was clamped and the hole was repaired with 7/O prolene suture. His further progress was uneventful and he was discharged seven days later.

Discussion

The placement of temporary epicardial pacemaker electrodes is routine in cardiac surgical practice and many surgeons use both atrial and ventricular wires.[1] The improved haemodynamic effects of sequential atrioventricular pacing and the potential for treating supraventricular arrhythmias with rapid atrial pacing are well recognised.[2]

We use a standard technique for fixing atrial epicardial electrodes. A 1 cm loop of bare wire is sutured high on the right atrial wall with a 6/O polypropylene (Prolene) and we prefer to site a second similar atrial wire rather than an indifferent electrode. This has been shown to be more useful for diagnostic purposes and also causes less distortion of the electrocardiogram by the stimulus artefact during pacing.[3] Several reports have emphasised the low complication rate with this implantation technique and subsequent removal of the wires by gentle traction.[3 4] Clinical and animal studies have not shown atrial bleeding to be an important problem[5] and we can find no previous report of graft injury during removal of a pacing wire.

Most ventricular electrodes can be sited on the anterior surface of the right ventricle remote from any grafts. Right atrial wires, however, often need careful positioning and this is a particular problem when two grafts are anastomosed proximally to the right aspect of the aorta.

Recognising the possibility of late injury, we now try to site the electrodes where they can be removed without jeopardising a graft. We also believe that the timing of removal is important. Our policy is to remove pacing wires early in the morning to permit observation throughout the day with optimum conditions for further investigation or operation. We never remove wires on the morning of discharge.

Requests for reprints to Mr Colin Price, FRCS, Cardiac Surgery Unit, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.

References

1 Waldo AL, Henthorn RW, Plumb VJ. Temporary epicardial wire electrodes in the diagnosis and treatment of arrhythmias after open heart surgery. *Am J Surg* 1984;**148**:275–83.

2 Friesen WG, Woodson RD, Ames AW, Herr RH, Starr A, Kassebaum DG. A haemodynamic comparison of atrial and ventricular pacing in postoperative cardiac surgical patients. *J Thorac Cardiovasc Surg* 1968;**55**: 271–9.

3 Waldo AL, MacLean WAH, Cooper TB, Kouchoukos NT, Karp RB. Use of temporarily placed epicardial atrial wire electrodes for the diagnosis and treatment of cardiac arrhythmias following open heart surgery. *J Thorac Cardiovasc Surg* 1978;**76**:500–5.

4 Mills NL, Ochsner JL. Experience with atrial pacemaker wires implanted during cardiac operations. *J Thorac Cardiovasc Surg* 1973;**66**:878–86.

5 Harris PD, Singer DH, Malm JR, Hoffman BF. Chronically implanted cardiac electrodes for diagnostic, therapeutic, and investigational use in man. *J Thorac Cardiovasc Surg* 1967;**54**:191–8.

Br Heart J 1989;**61**:548–50

Severe haemolysis after percutaneous closure of a ductus arteriosus (arterial duct)

E J LADUSANS,* I MURDOCH,* J FRANCIOSI†

*From the Departments of *Paediatric Cardiology and †Cardiothoracic Surgery, Guy's Hospital London*

SUMMARY Severe mechanical haemolysis occurred after transcatheter occlusion of a ductus arteriosus (arterial duct) by a Rashkind double umbrella prosthesis. Surgical removal of the device and ligation of the duct were required before haemolysis was abolished.

Transcatheter occlusion of the ductus arteriosus (arterial duct) was first reported by Porstmann *et al*, who used a wire and plug technique.[1] Subsequently Rashkind *et al* developed a double umbrella prosthesis[2] and showed that this could be used successfully to close the arterial duct.[3] Complications described from this procedure include arterial or pulmonary embolisation of the device and residual duct leaks.[3 4] We describe a hitherto unreported hazard—that of severe haemolysis after insertion of the Rashkind occluder.

Case report

A symptom free two and a half year old girl was found to have a heart murmur on a routine examination. A continuous murmur was heard below the left clavicle and echocardiography confirmed an arterial duct and normal intracardiac structure. The parents agreed to have the defect closed by percutaneous technique. This was carried out by the method of Bash and Mullins.[5] A preliminary aortogram through a retrograde arterial catheter defined the anatomy of the duct and showed that it measured 3 mm at the narrowest point (fig 1). An 0·038 exchange guide wire (William Cook Europe) was passed through a venous catheter into the descending aorta via the duct. An 8 French Mullins transseptal sheath (William Cook Europe) was then passed over the guide wire into the descending aorta. A 12 mm Rashkind double umbrella prosthesis (USCI, Billerica, MA) was passed through a Rashkind delivery catheter into the Mullins sheath. The device was advanced so that the distal umbrella opened in the aorta. The whole system, including the sheath, was then slowly pulled back until the distal umbrella was well seated in the aortic end of the duct. The sheath was then retracted further so that the proximal umbrella could spring open and secure the device at the pulmonary end of the duct. The device was released and we noted that the prosthesis had been pulled a little too far towards the pulmonary end of the duct (fig 2a). A repeat aortogram showed that there was a considerable leak through the duct around the device (fig 2b). The apparent increase in size of the duct was caused by changes in magnification and true dilatation of the duct by the passage of the 8 French transseptal sheath and delivery catheter.

Eighteen hours after insertion of the prosthesis she began to pass heavily bloodstained urine and was jaundiced. Microscopical examination of the urine showed haemoglobin but no red blood cells. The blood haemoglobin fell from 110 g/l pre-catheter to

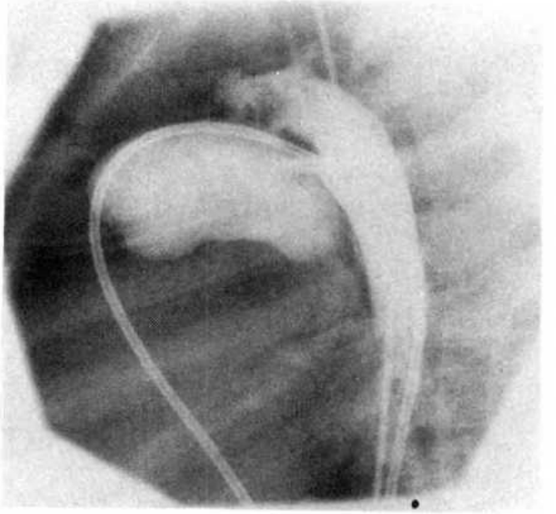


Fig 1 *Initial aortogram showing arterial duct.*

Requests for reprints to Dr E J Ladusans, Department of Paediatric Cardiology, Guy's Hospital, St Thomas Street, London SE1 9RT.

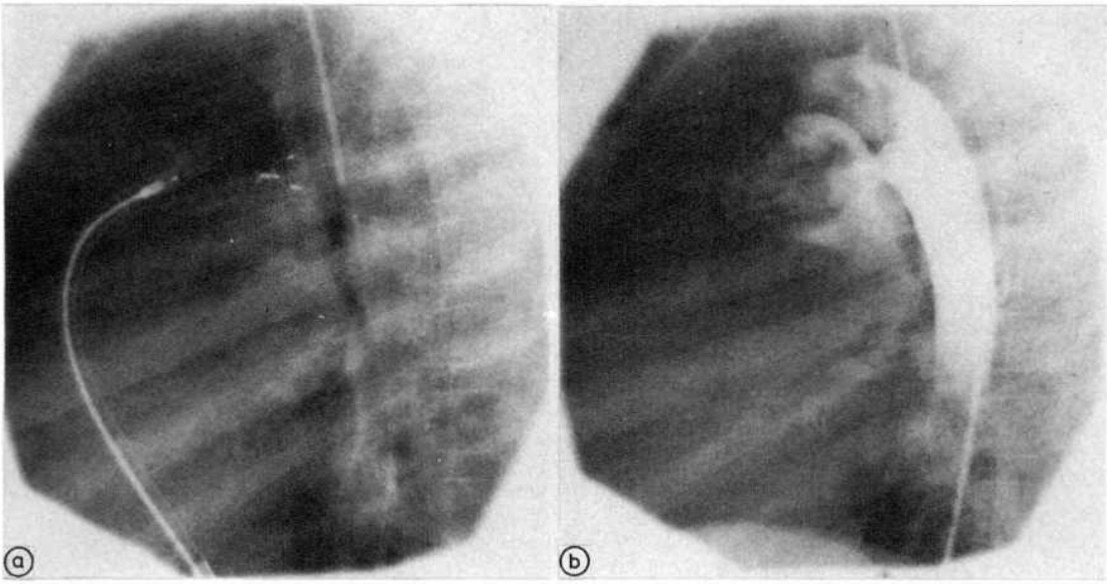


Fig 2 *(a) Lateral radiograph after release of the device. The proximal umbrella (faintly radio-opaque prongs) was positioned too far into the pulmonary artery. (b) Aortogram after implantation of the device. Residual flow was seen through the arterial duct and around the device.*

79 g/l. There was a progressive reticulocytosis and a blood film showed evidence of red cell fragmentation. Blood cultures were negative.

A repeat echocardiogram showed that the proximal umbrella was situated further into the pulmonary artery than is usual and there was clot around the umbrella. Doppler examination confirmed a residual leak through the duct. The haemolysis was initially treated conservatively with blood transfusions to correct her anaemia. After 72 hours there was no decrease in red cell destruction and blood haemoglobin had fallen again to 74 g/l. She was referred for urgent surgical removal of the device and duct ligation. At operation the main pulmonary artery was cross clamped and the descending aorta side clamped at the origin of the arterial duct. The duct was incised longitudinally and the occluder retrieved. The prosthesis had not been damaged and there was no evidence of infection. The duct was then oversewn and ligated with linen sutures. Postoperative recovery was uneventful with no further haemolysis and the blood haemoglobin concentrations was maintained at 130 g/l.

Discussion

The Rashkind occluder consists of two discs mounted on two opposing three arm spring assemblies. The whole device resembles two connected umbrellas.[6] Each disc is constructed from open-pore polyurethane foam and though initially blood can leak through this mesh, animal experiments have shown that the discs rapidly become endothelialised. They are eventually covered with tissue and incorporated into the arterial walls.[3] We postulate that in our patient severe haemolysis occurred because the prosthesis was implanted with the proximal umbrella too far into the pulmonary artery. This resulted in a residual leak through the duct and around the device with a high velocity jet of blood directed on to the mesh of the proximal disc and consequent damage to the red cells.

Rashkind *et al* reported an initial experience of this device in 146 patients.[3] There was systemic or pulmonary embolisation of the device immediately after its release in 13% of patients. Ten per cent of patients had evidence of residual flow despite successful implantation of the occluder. Perry *et al* found similar results in 28 patients—with four embolisations and four patients with considerable residual leak.[4] Dyck *et al* treated 40 patients with the duct occluder.[7] There were two embolisations and 21% of patients had a residual leak. One patient developed staphylococcal septicaemia after insertion of the device and probable prosthetic endartritis. MJ Tynan at Guy's Hospital has experience of 70 implantations. Two devices embolised and there was residual flow in the duct in four patients (personal communication). To our knowledge severe haemolysis after insertion of a Rashkind prosthesis has not previously been reported; it is a serious potential hazard of residual duct flow with a malpositioned device.

We thank Professor Michael Tynan for allowing us to report on a patient under his care.

References

1 Porstmann W, Wierney L, Warnke H, Gerstberger G, Romanuik PA. Catheter closure of patent ductus arteriosus: 62 cases treated without thoracotomy. *Radiol Clin North Am* 1971;9:203–18.
2 Rashkind WJ, Cuaso CC. Transcatheter closure of patient ductus arteriosus. *Pediatr Cardiol* 1979;**1**:3–8.
3 Rashkind WJ, Mullins CE, Hellenbrand WE, Tait MA Nonsurgical closure of patent ductus arteriosus: clinical application of the Rashkind PDA occluder system. *Circulation* 1987;75:583–92.
4 Perry SB, Keane JF, Lock JE. Interventional catheterisation in pediatric congenital and acquired heart disease. *Am J Cardiol* 1987;**61** (suppl): 109G–17G.
5 Bash SE, Mullins CE. Insertion of patent ductus occluder by transvenous approach: a new technique [Abstract]. *Circulation* 1984;**70** (suppl II):285.
6 Rashkind WJ. Transcatheter treatment of congenital heart disease. *Circulation* 1983;67:711–6.
7 Dyck JD, Benson LN, Smallhorn JF, McLaughlin PR, Freedom RM, Rowe RD. Catheter occlusion of the persistently patent ductus arteriosus. *Am J Cardiol* 1988;**62**:1089–92.

Br Heart J 1989;61:551–3

Percutaneous transluminal balloon dilatation of the mitral valve in pregnancy

ROBERT SMITH, DAVID BRENDER, MICHAEL McCREDIE

From the Department of Cardiovascular Medicine, Prince Henry and Prince of Wales Hospitals, and the Department of Medicine, Royal Hospital for Women, Sydney, New South Wales, Australia

SUMMARY Pregnancy can cause life threatening complications in women with mitral stenosis, and there is a substantial risk of fetal death if valvotomy under cardiopulmonary bypass is required. A patient is described in whom pulmonary oedema developed after delivery of her first child by caesarean section 13 months previously. Subsequent cardiac catheterisation showed severe mitral stenosis (valve area 0·96 cm^2, valve gradient 12 mm Hg, pulmonary artery pressure 30/16 mm Hg). Before valvotomy could be performed the patient again became pregnant and presented in pulmonary oedema at twenty two weeks' gestation. Medical treatment was unsuccessful and she underwent percutaneous transluminal balloon dilatation of the mitral valve. This increased the valve area to 1·78 cm^2 and reduced the transmitral gradient to 6 mm Hg. The procedure was uncomplicated, and she remained symptom free on no medication. She delivered vaginally at 37 weeks' gestation.

Percutaneous transluminal balloon dilatation of the mitral valve is a safe and effective alternative to mitral valvotomy in pregnancy.

Patients with mitral stenosis have an impaired cardiovascular response to the altered haemodynamic function of pregnancy. The increased cardiac output as well as the tachycardia,[1] which leads to a shortened diastolic filling period, aggravates the already impeded effective left atrial emptying. This increases the left atrial pressure, especially on exertion, and results in pulmonary oedema. While the tachycardia can often be slowed by β blockade, this may not be sufficient, and valvotomy may be required during pregnancy. This often requires cardiopulmonary bypass and is associated with high fetal morbidity and mortality.[2] The technique of percutaneous transluminal balloon mitral dilatation of the valve offers a safer alternative to surgical valvotomy and we report here a women who had balloon dilatation of the mitral valve at 23 weeks' gestation.

Case report

This 29 year old woman had a history of rheumatic fever at the age of 11. She had had an uneventful pregnancy 13 months previously. She was delivered by elective caesarean section for obstetric indications (prolonged labour with failure to progress), but immediately after the caesarean section she went into acute pulmonary oedema. She responded to medical treatment with frusemide and digitalis, and three months later underwent cardiac catheterisation, which showed severe mitral stenosis (mitral valve gradient 12 mm Hg and mitral valve area 0·96 cm^2, pulmonary artery pressure 30/16 mm Hg). Ventriculography showed mild mitral regurgitation.

Valvotomy was advised but while she was considering this advice she became pregnant again. She remained well until about 22 weeks' gestation when she presented with a cough and functional class II dyspnoea. Physical examination showed signs of severe mitral stenosis with pulmonary hypertension. A Doppler echocardiogram showed a gradient of 14 mm Hg across the mitral valve and a valve area estimated at 1·1 cm^2, with mild mitral regurgitation. She was admitted to hospital and treated with a diuretic (frusemide 40 mg daily) and a β blocker (metoprolol 50 mg twice a day).

Though metoprolol slowed her exertional tachycardia, her symptoms remained severe and she progressed to functional class III. She was intolerant of larger doses of metoprolol because of hypotension

Requests for reprints to Dr David Brender, The Medical Centre, Second Floor, 64 High Street, Randwick, NSW 2031, Australia

(supine blood pressure 90/70 mm Hg) and postural symptoms during normal mobility in the ward.

After four days it became apparent that she was not responding to medical treatment, and she underwent percutaneous transluminal balloon mitral dilatation of the valve at 23 weeks' gestation.

METHODS

We successfully dilated the mitral valve under local anaesthesia, using the technique previously described.[3] A double balloon system was used—one trefoil (3 × 10 mm diameter) and one monofoil (15 mm) balloon. The two balloons were positioned across the mitral valve and inflated twice until a good angiographic result was obtained with obliteration of the indentation made on the balloon by the mitral apparatus. We shielded the uterus with lead and used the shortest practicable screening time. A colloid infusion was given as a rapid bolus at the time of balloon inflation to prevent systemic hypotension.

RESULTS

The mean gradient across the mitral valve fell from 14 mm Hg to 6 mm Hg and the mitral valve area increased from 0·95 cm^2 to 1·78 cm^2. The cardiac output increased from 4·5 l/min to 5·5 l/min. Ventriculography at the end of the procedure showed that the mild degree of mitral regurgitation remained unchanged. Measurement of oxygen saturations in the right heart showed that there was no shunt from the atrial septostomy. An hour after dilatation transient (< 1 h) right bundle branch block developed. A Doppler echocardiography study done 24 hours after the procedure confirmed the improvement in the valve variables (valve area 1·7 cm^2). She was discharged from hospital 36 hours after the procedure, and resumed her normal activity. She remained symptom free throughout the remainder of her pregnancy, and delivered vaginally at 37 weeks.

Discussion

Normal cardiovascular adaptation in pregnancy in patients with a stenosed mitral valve is limited by the associated physiological increase in resting heart rate and a shortened diastolic filling time. This leads to increased left atrial pressure and dyspnoea, especially on exertion, and may threaten both mother and fetus. The tachycardia is of sinus origin and is unresponsive to digoxin because the increased sympathetic tone in pregnancy overrides the vagal effect of digoxin. β Blockade is often effective in slowing the exertional tachycardia in these patients, and may allow pregnancy to continue without the need for valvotomy. However, our patient was not able to tolerate a dose of metoprolol sufficient to prevent tachycardia because unacceptable hypotension developed at a low dose (50 mg twice a day). With open valvotomy, which requires cardiopulmonary bypass, the fetal mortality ranged from 15% to 33%.[2 4] Also the risk of teratogenesis was increased probably due to the use of high dose heparin and hypothermia; such a risk is particularly important during the first trimester.[2] With closed valvotomy, which does not require cardiopulmonary bypass, fetal mortality was 12% to 15%[4]; this operation is rarely performed nowadays in Australia.

Experience of percutaneous transluminal balloon dilatation of the mitral valve during pregnancy is limited.[5 6] The procedure was performed rapidly, with minimal screening time and lead shielding of the uterus. It was tolerated well by the patient. The result was excellent, with an increase in valve area and decrease in valve gradient.

She developed transient right bundle branch block an hour after the procedure. This lasted for about an hour and then the rhythm spontaneously reverted to normal. This effect has been described in other patients treated by percutaneous transluminal balloon dilatation of the mitral valve and is probably caused by transient dysfunction of the right bundle related to the catheters, balloons, and guidewires used during the procedure which can lie against the right bundle. She became almost symptom free immediately on return to the ward, and was discharged from hospital 36 hours later, on a tapered dose of metoprolol. She remained symptom free without medication, and maintained a normal level of activity until a normal vaginal delivery at 37 weeks.

CONCLUSIONS

This case illustrates four major points: (*a*) The life threatening nature of severe mitral stenosis in pregnancy and the urgent need to increase the mitral valve area mechanically. (*b*) The likelihood that medical treatment will fail because of the altered haemodynamic state in pregnancy. Conventional treatment for mitral stenosis is often ineffective. (*c*) Preconception counselling, which was offered to this patient, is of vital importance to women with valve disease if the need for emergency procedures is to be avoided. (*d*) Percutaneous transluminal balloon dilatation of the mitral valve is a safe and effective alternative to surgical valvotomy in the management of mitral stenosis during pregnancy.

References

1 Szekely P, Snaith L. *Heart disease and pregnancy*. Edinburgh and London: Churchill Livingstone, 1974.

2 Vosloo S, Reichart B. The feasibility of closed mitral

valvotomy in pregnancy. *Thorac Cardiovasc Surg* 1987;93:675–9.

3 Lock J, Khalilullah M, Shrivasta S. Percutaneous catheter commissurotomy in rheumatic mitral stenosis. *N Engl J Med* 1985;313:1515–8.

4 Goon M, Raman S, Sinnathuray T. Closed mitral valvotomy in pregnancy. *Aust NZ J Obstet Gynaecol* 1987;27:173–7.

5 Safian R, Berman A, Sachs B, *et al.* Percutaneous balloon mitral valvuloplasty in a pregnant woman with mitral stenosis. *Cathet Cardiovasc Diagn* 1988;15:103–8.

6 Palacios I, Block P, Wilkins G, Rediker D, Daggett W. Percutaneous mitral balloon valvotomy during pregnancy in a patient with severe mitral stenosis. *Cathet Cardiovasc Diagn* 1988;15:109–11.

Notices

British Cardiac Society

The Annual General Meeting will take place in Torquay on 22 to 25 May 1990.

Atrial arrhythmias

A meeting on Current Concepts in the Study and Management of Atrial Arrhythmias will be held in Lyon on 6 to 8 December 1989. For further information write to PMV Congres/Arythmies 89, 130 rue de Clignancourt, 75018 Paris, France.

Br Heart J 1989;61:554

Correspondence

Demonstration of the ascending aorta in infective endocarditis by intravenous digital subtraction angiography

Sir,

We read with interest the article by Hunter *et al* (1988;60:252–8).

There seems to be some confusion in published reports about the terminology of the aortic root complications encountered in infective endocarditis. An abscess is an infective cavity that is completely enclosed, with no communication with the intravascular space. A mycotic aneurysm, however, is defined as a cavity that does communicate with the vascular space, and it usually results from the rupture of an abscess cavity into the vascular space. Further rupture into a second but different vascular space results in the formation of an infective fistula. The terminology of these lesions is important because only mycotic aneurysms and fistulas can potentially be shown by angiographic techniques, including intravenous digital subtraction angiography. Abscess cavities would be missed by both these techniques. The four cases reported in this article are therefore mycotic aneurysms and not endocarditis abscesses, as described.

Hunter *et al* have also overlooked the importance of echocardiography in the diagnosis of aortic root involvement by infective endocarditis. We accept that precordial cross sectional echocardiography is unreliable in the diagnosis of aortic root abscesses and mycotic aneurysms, especially when prosthetic valves are present. Transoesophageal cross sectional echocardiography, because of its improved image quality and resolution, has recently proved more sensitive in the diagnosis of these complications than precordial echocardiography.[1-3] The addition of colour flow mapping also provides important information because it can distinguish between abscess cavities and mycotic aneurysms by showing flow entering or exiting the cavity in question. Colour flow mapping is also a good diagnostic technique for showing the presence and precise delineation of any intracardiac infective fistulas.

Transoesophageal echocardiography is a safe procedure, even in acutely ill patients, which has been in routine diagnostic use in over 700 cases at the Thoraxcentre since 1985. Our experience using this technique in a wide range of patients with infective endocarditis is that it increases the diagnosis of aortic root complications compared with precordial echocardiography. We have noted only one area where the usefulness of transoesophageal echocardiography is limited, and that is in the detection of anterior aortic root cavities in patients with aortic prostheses. These may be missed by the transoesophageal approach because of the image "masking effect" of the prosthetic valve. In these cases the anterior cavities are usually visualised by the precordial approach.

In view of our experience and that of others,[2 3] we recommend that transoesophageal echocardiography is mandatory in all patients with suspected endocarditis of a native or prosthetic aortic valve because it is the best diagnostic method for the infective complications.

John H Smyllie,
George R Sutherland,
Jos R T C Roelandt,
Thoraxcentre, Ba302,
Academic Hospital-Dijkzigt,
Rotterdam, The Netherlands.

References

1 Gussenhoven EJ, van Herverden LA, Roelandt J, Bos E, de Jong N. Detailed analysis of aortic valve endocarditis: comparison of precordial, esophageal and epicardial two-dimensional echocardiography with surgical findings. *JCU* 1986;14:209–11.

2 Drexler M, Erbel R, Rohmann S, Mohr-Kahaly S, Meyer J. Diagnostic value of two-dimensional transesophageal versus transthoracic echocardiography in patients with infective endocarditis. *Eur Heart J* 1987;8 (suppl I):303–6.

3 Daniel WG, Schroeder E, Moegge A, Lichtlen PR. Transesophageal echocardiography in infective endocarditis. *Am J Cardiac Imaging* 1988;2:78–85.

NATIONAL UNIVERSITY OF SINGAPORE
DEPARTMENT OF SURGERY

Applications are invited for appointment as Teaching Fellow in the Department of Surgery for one year, in the first instance. Candidates should possess an approved basic medical degree and relevant postgraduate qualifications. Preference will be given to those with experience in cardiothoracic surgery.

The appointee will be required to teach at the undergraduate and postgraduate levels. There will be opportunities for active clinical practice in adult and congenital open heart, thoracic and vascular surgery with experimental surgical research.

Gross annual emoluments range from S$47,630–58,680. (STG1.00 = S$3.29 approx.)

The commencing salary will depend on the candidate's qualifications and experience. In addition to the salary offered, appointees may receive a fixed annual clinical allowance of S$6,000/9,000.

Leave and medical benefits will be provided. Depending on the type of contract offered, other benefits may include: provident fund benefits or an end-of-contract gratuity, a settling-in allowance of S$1,000 or S$2,000, subsidised housing at nominal rentals ranging from S$100 to S$216 p.m., education allowance for up to three children subject to a maximum of S$10,000 per annum per child, passage assistance and baggage allowance for the transportation of personal effects to Singapore.

The Department of Surgery is a department in the Faculty of Medicine. There are 8 faculties in the National University of Singapore with a current student enrolment of some 14,000. All departments are well-equipped with a wide range of facilities to enhance the teaching and research activities of staff members. The University is linked to BITNET, an international network that interconnects almost 500 mainframe computers at 200 institutions of higher learning and research centres around the world.

Application forms and further information on terms and conditions of service may be obtained from:

The Director
Personnel Department
National University of Singapore
10 Kent Ridge Crescent
Singapore 0511

NUS Overseas Office
Singapore High Commission in London
5 Chesham Street
London SW1, U.K.
Tel: (01) 235-4562

Enquiries may also be sent through BITNET to: **PERSDEPT @ NUSVM**

STATISTICS WITH CONFIDENCE
– Confidence intervals and statistical guidelines
MARTIN J GARDNER
DOUGLAS G ALTMAN
BMJ

Just published

Many medical journals, including the *British Medical Journal,* now expect scientific papers submitted to them to contain confidence intervals when appropriate. Why? what are they? and how do you calculate them? *Statistics with Confidence* tells you. A clear explanation of the reasons for using confidence intervals is followed by detailed presentation of methods of calculation, including numerous worked examples and specially compiled tables. To make things even easier, a computer programme, Confidence Interval Analysis (CIA), for calculating confidence intervals, has been specially designed by Martin Gardner and details are available from the Publishing Department, *British Medical Journal.*

Price: Inland £7.95;
Abroad £9.50
BMA members: Inland £7.45;
Abroad: £9.00

Eighth edition

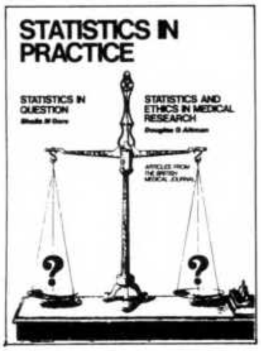
The statistical testing of data is indispensable in many types of medical investigation and a help on countless occasions in clinical practice. This book provides step by step instruction. Subjects covered include standard deviation, χ^2 tests, t tests, non-parametric tests, and correlation. The book includes sections on Fisher's exact probability test and rank correlation not published in the original *BMJ* series. Methods specially adapted to pocket calculators.

Price: Inland £3.00;
Abroad £4.50
BMA members: Inland £2.50;
Abroad: £4.00

"He uses statistics as a drunken man uses lamp-posts — for support rather than illumination." *

Let the *BMJ* throw light on your methods and help your results stand up

* *Andrew Lang*


STATISTICS IN PRACTICE
STATISTICS IN QUESTION
Sheila M Gore
STATISTICS AND ETHICS IN MEDICAL RESEARCH
Douglas G Altman
ARTICLES FROM THE BRITISH MEDICAL JOURNAL
?
?

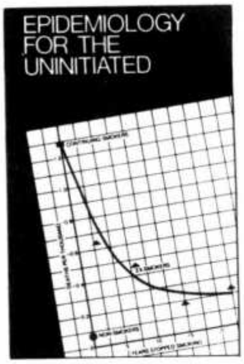
Fourth impression

No doctor can afford to ignore statistics: most modern medical research uses statistics. This important and authoritative book provides clear information on designing studies, applying statistical techniques, and interpreting studies that use statistics. It can be easily understood by those with no statistical training and should be read by all those who want to keep abreast of new developments.

Price: Inland £8.95;
Abroad £11.00
BMA members: Inland £7.45;
Abroad: £10.00

Second edition

Epidemiology has its own techniques of data collection and interpretation and its necessary jargon of technical terms, and in *Epidemiology for the Uninitiated* Professors Geoffrey Rose and David Barker guide the novice expertly through the theory and practical pitfalls. The second edition of this popular *BMJ* handbook has been revised to include further details of epidemiological methods and some of their more dramatic applications, such as the investigations on the Spanish cooking oil epidemic, and AIDS.



Price: Inland £3.95;
Abroad £5.50
BMA members: Inland £3.45;
Abroad: £5.00

ORDER FORM

BRITISH MEDICAL JOURNAL, P.O. Box 295,
London WC1H 9TE, England *or any leading medical bookseller*

Please send me
☐ Statistics with Confidence
☐ Statistics at Square One
☐ Statistics in Practice
☐ Epidemiology for the Uninitiated
All prices include postage, by air abroad

NAME ....
ADDRESS ....
....
POSTCODE ....

I enclose .... BMA Membership No. ....

Please make cheques payable to **British Medical Journal** o debit my credit card (please tick box)

☐ Access/Mastercard ☐ Barclaycard/Visa
☐ American Express

Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

CARD EXPIRY DATE ....
SIGNATURE ....
☐ Please send me a book catalogue

Br Heart J 1989;**61**:555–6

List of advisers

We thank the following who have reviewed manuscripts submitted to the British Heart Journal during 1988.

C P Aber
L D Allan
J Anderson
R H Anderson
T Ashcroft
R Balcon
D Ballantyne
M Ballester
J Bayliss
A E Becker
W M H Behan
J S Birkhead
P Bloomfield
N A Boon
M V Braimbridge
N Brooks
A K Brown
C Bucknall
C Bull
J Burn
J E Burns
C Burrell
A J Camm
R W F Campbell
D A Chamberlain
S Chierchia
A H Child
J Cleland
S M Cobbe
P Colvin
P Coumel
J C Cowan
J N Cox
T Cox
T Cripps
D C Cumberland
P Cummins
J Cunningham
S D Cunningham
P V L Curry
C M Dancy
H J Dargie
K G Davidson
D W Davies
G J Davies,
J Davies
K D Dawkins
R Dawson
J E Deanfield
M de Belder
D P de Bono
P B Deverall
D F Dickinson
D S Dymond
T A H English
S J W Evans
S J Eykyn
J T Fallon
J S Fleming
R A Foale
K A A Fox
L Freeman
M P Frenneaux
P J Gallagher
M D Gammage
A M Garson
A Gershlick
J L Gibbs
D G Gibson
M J Godman
J F Goodwin
H H Gray
R A Greenbaum
B Gribben
G Griffin
M J Griffith
T E Guiney
D Hackett
R J C Hall
P S Hasleton
S G Haworth
D A Heath
A H Henderson
A M Henney
G Hitman
Y Ho
A Hollman
P Holt
M Honey
A B Houston
W N Hubbard
P Hubner
G V Hunter
S Hunter
I Hutton
C Ilsley
G Jackson
H S Joffe
S Joseph
M D Joy
E L Kaplan
B Keeton
B Z Khan
F J Klocke
M F Knapp
S B Knoebel
J P Kopelman
G Laszlo
A Leatham
G Leech
N Linker
D Lipkin
W A Littler
P J Lowry
F J Macartney
P Magee
P Markman
M Marmot
A Martin
R McKay
W J McKenna
T W Meade
G A H Miller
H C Miller
J R Milne
M J Monaghan
J L Monro
J P Monson
A L Muir
R G Murray
A W Nathan
R Nicholson
M I M Noble
P Nihoyannopoulos
C M Oakley
G D G Oakley
P J Oldershaw
E G J Olsen
D J Parker
R G Patel
B L Pentecost
J Pepper
M S Perelman
J Perrins
M C Petch
P A Poole-Wilson
C R N Prentice
F Preston
C Pumphrey
S A Qureshi
M Raphael
J M Rawles
D Redwood

C Reismer
P Richardson
A F Rickards
R Riemersa
M L Rigby
B F Robinson
K Robinson
E Robles de Medina
S Rosalki
G A Rose
M T Rothman
E Rowland
D J Rowlands
O Scott
A Selzer
A G Shaper
L M Shapiro
D B Shaw
M Sheppard
E A Shinebourne
M F Shiu
A J Silman
E D Silove
D Skorton
E E J Smith
J Somerville
C J Spry
R Steiner
B Surawicz
G C Sutton
R Sutton
R H Swanton
M Swash
D Syndercombe-Court
P Taggart
A C Thomas
G R Thompson
A D Timmis
T Treasure
H Tunstall-Pedoe
A C Tweddel
S R Underwood
R J Vecht
D W Vere
R K Walesby
J M Walker
B Waller
M J Walport
D Ward
J Watkins
S W Webb
M Webb-Peploe
S Westaby
J Wharton
D Wheatley
P T Wilmshurst
N Woolf
K J Zilkha

AUTHOR INDEX
1989, Volume 61

P = Proceedings of the British Cardiac Society

Abdulla A K *see* Mohiaddin R H *et al*

Abinader E G (& Sharif D S) Influence of age on Doppler echocardiographic indices of left ventricular diastolic function: correspondence 483

Adams K M *see* McKenna W J *et al*

Adams S *see* Nevin M *et al*

Adgey A A J *see* Dalzell G W N *et al*
  Dickey W *et al*
  McKeown P *et al*
  McKeown P P *et al*
  McNeil A J *et al*

Agarwal A K (& Redding V J) Transvenous His bundle ablation: short term and long term (6·36 months) results in 15 patients. Can success be predicted? 99 *P*

Ahmad R A S (& Sturman S, Watson R D S) Unruptured aneurysm of the sinus of Valsalva presenting with isolated heart block: echocardiographic diagnosis and successful surgical repair: case report 375

Ahmed A *see* Mittal R B *et al*

Akhras F (& Jackson G) Prediction of outcome after acute uncomplicated myocardial infarction: a study of 394 patients with five year follow up 120*P*

— *see also* Wordsworth P *et al*

Albers C *see* Peart I *et al*

Alfonso F (& Frenneaux M P, McKenna W J) Clinical sustained uniform ventricular tachycardia in hypertrophic cardiomyopathy: association with left ventricular apical aneurysm 178

Aliot E *see* Brembilla-Perrot B *et al*

Allan L *see* Parsons J M *et al*
  Virginia M *et al*

Allen D C *see* Richardson S G *et al*

Allen J *see* Sprigings D C *et al*

Allen J D *see* McKeown P *et al*

Al-Riyami A (& Macfarlane P W, Cobbe S M) Prevalence of ventricular arrhythmias in patients with left ventricular hypertrophy caused by aortic valve disease 450 *P*

Amano A *see* Toyama M *et al*

Ambepityia G (& Kopelman P G, Ingram D, MacDonald R, Mills P G, Timmis A D) The perception of angina in diabetic patients: evidence of silent exertional ischaemia 437 *P*

Andersen H R (& Falk E, Nielsen D) Right ventricular infarction: diagnostic accuracy of electrocardiographic right chest leads V3R to V7R investigated prospectively in 43 consecutive fatal cases from a coronary care unit 514

Anderson D *see* Pepper J R *et al*

Anderson J *see* Dalzell G W N *et al*
  Dickey W A *et al*
  McKeown P *et al*
  McKeown P P *et al*

Anderson R H *see* Carvalho J S *et al*
  Franklin R C G *et al*
  Parsons J M *et al*
  Wharton J *et al*

Andreotti F (& Davies G J, Maseri A, Hamilton J, Hopkins N, Mansfield A, Kluft C) Evidence for increased tissue type plasminogen activator inhibitor complexes in atherosclerotic patients 100 *P*

— *see also* Khan M I *et al*

Angelini G (& Hazekamp M, Van Boven V, Huysmans H, Quaegebeur J) Symmetrical aortoplasty repair for supravalvar aortic stenosis 482 *P*

Angelini G D (& Soyombo A, Bryan A J, Newby A C) Intimal proliferation in an organ culture of human saphenous vein 108 *P*

— *see also* Bryan A J *et al*

Antoniou A *see* Garratt C J *et al*

Aranki S (& Pilai R, Khaghani A, Dhalla N, Tajkarimi S, Musumeci F, Aravot D, Yacoub M H) An evaluation of homovital aortic valve homografts 126 *P*

Aravot D (& Banner N, Khaghani A, Fitzgerald M, Musumeci F, Radley-Smith R, Yacoub M H) Cardiac transplantation in patients with present or past malignant neoplasms 464 *P*

— *see also* Aranki S *et al*

Archard L C (& Banner N R, Bowles N E, Freeke C, Meany B T, Olsen E G, Richardson P J, Rose M, Yacoub M H) Enterovirus RNA in myocardium of patients with dilated cardiomyopathy 73 *P*

Armstrong A P *see* Barin E S *et al*

Arnold R *see* Walsh K P *et al*

Arnolda L (& Conway M, Dolecki M, Sharif H, Sleight P, Ledingham J, Radda G K, Rajagopalan B) Phosphorus magnetic resonance spectroscopy of leg muscle in heart failure 459 *P*

Aronson J K *see* Pugh S E *et al*

Ashley *see* Gehani A A *et al*

Au P *see* Bhandari A K *et al*

Aylward P E *see* Smith S A *et al*

Ayton V *see* Baker E J *et al*
  Parsons J M *et al*

Badimon L *see* Penny W J *et al*

Baig M W (& Cowan J C, Cant J, Perrins E J) Electrophysiological basis of the configurations of the ventricular paced evoked response 473 *P*

Bailey A *see* Dickey W A *et al*

Bailey J *see* Davies S *et al*
  Davies S W *et al*

Bain H *see* Sullivan I D *et al*

Bain W *see* Pye M *et al*

Baird I *see* DasGupta P *et al*

Baker E J (& Parsons J M, Ladusans E J, Ayton V, Smith M A, Maisey M N, Tynan M J) Magnetic resonance imaging of the great arteries in infants 75 *P*

— *see also* Ladusans E J *et al*
  Parsons J M *et al*

Balaji S (& Keeton B R, Sutherland G R, Shore D F, Monro J L) Aortic valvotomy for critical aortic stenosis in neonates and infants aged less than one year 358

Balcon R (& Rothman M, Gershlick A, Layton C, Mishra A) Effect of initial lesion type on the results of coronary angioplasty 446 *P*

— *see also* Davies S *et al*
  Davies S W *et al*
  Gershlick A H *et al*
  Norell M S *et al*

Ballantyne D *see* Northcote R J *et al*
  Todd I C and Ballantyne D

Banner N *see* Aravot D *et al*

Banner N R (& Lloyd M H, Hamilton R D, Innes J A, Guz A, Yacoub M H) Cardiopulmonary response to dynamic exercise after heart and combined heart-lung transplantation 215

— (& Patel N, Cox A, Patton H, Lachno D R, Yacoub M H) Sympathetic neurohormonal response to dynamic exercise early after orthotopic cardiac transplantation 127 *P*

Banner N R *see* Archard L C *et al*

— *see also* Barbir M *et al*
Barbir M (& Banner N R, Reid C J, Thompson G R, Mitchell A G, Yacoub M H) Influence of lipid abnormalities on the development of coronary arterial disease after cardiac transplantation 462 *P*
— *see also* Taha T H *et al*
Barin E S (& Macpherson P C, Ho S Y, Waterfield S A, Armstrong A P, Nathan A W) Observations on tissue changes and arcing with multiple high voltage low energy shocks for electrode catheter mediated cardiac ablation 469 *P*
— *see also* Davies D W *et al*
  Ratnatunga C P *et al*
Barrett C W *see* Skehan J D *et al*
Beatt K J (& Luijten H E, Suryapranata H, de Feyter P J, Serruys P W) Dilatation variables: the paradox of optimal improvement in stenosis by percutaneous transluminal coronary angioplasty and restenosis 439 *P*
— (& Kamp O, Suryapranata H, Geuskens R, Serruys P W) Stent implantation for the treatment of coronary artery bypass graft stenosis 446 *P*
Beattie J *see* Hunt A C *et al*
Beattie J M *see* Fox J P *et al*
Been M *see* Goudevenos J *et al*
Beggs O *see* Dickey W A *et al*
Belch J *see* McMurray J *et al*
Belder M DE *see* de Belder M
Bell M *see* Penny W J *et al*
Bell M R (& Holmes D R, Vlietstra R E, Bresnahan D R) Percutaneous transluminal angioplasty of left internal mammary artery grafts: two years' experience with a femoral approach 417
Belz G G *see* de Mey C & Belz G G
Bennett D H *see* Molajo A O *et al*
Benson L N *see* Ino T *et al*
  Leung M P *et al*
Bergman G (& Meany B, Metcalfe J, Thomas S, Jackson G, Jewitt D E) Simple and complex coronary angioplasty with a Monorail system 447 *P*
— (& Smyth D, Meany B, Thomas S, Forsyth A, Jackson G, Jewitt D E) Angioplasty of bifurcation lesions in major coronary vessels 84 *P*
Bergmann S R *see* Fox K A A *et al*
Bexton R *see* Robson R H *et al*
Bexton R S *see* Robson S C *et al*
Bhandari A K (& Hong R, Kotlewski A, McIntosh N, Au P, Sankooikal A, Rahimtoola S H) Prognostic significance of programmed ventricular stimulation in survivors of acute myocardial infarction 410
Bhate M *see* Sreeram N *et al*
Bidstrup B P (& Royston D, Sapsford R N, Taylor K M) Effect of aprotinin on blood conservation during cardiac surgery 111 *P*
Black F (& Foley B, Crean P, Walsh M) Cardiac rehabilitation after open heart surgery: a surprising fact 448 *P*
Black M M *see* Sprigings D C *et al*
Blackie R A S *see* Keogh B E *et al*
Blackledge M J *see* Conway M *et al*
Blake D R *see* Burrell C J & Blake D R
Bleasdale C *see* Higham P D *et al*
Blomstrom-Lundqvist C (& Caidahl K, Olsson S B, Rudin A) Electrocardiographic findings and frequency of arrhythmias in Bartter's syndrome 274
Bloomfield J G *see* Pugh S E *et al*
Bloomfield P (& Wheatley D J, Prescott R J, Miller H C) Ten year results of a randomised trial of the Bjork-Shiley, Hancock, and Carpentier-Edwards prostheses 452 *P*
Boden W E (& Kleiger R E, Gibson R S, Reddy B R, Schechtman K B, Schwartz D J, Capone R J, Roberts R, Diltiazem Reinfarction Study Research Group) Favourable long term prognosis in patients with non-Q wave acute myocardial infarction not associated with specific electrocardiographic changes 396
Bom N *see* Taams M A *et al*
Bonifacio E *see* Caforio A *et al*
Bonser R S (& Fragomeni L S, Jamieson S W, Kaye M P) Deleterious effects of prostaglandin E1 in 12 hour lung preservation 463 *P*
— *see also* Luke R A *et al*
Boon N A *see* Winner S J & Boon N A
Bos E *see* Fraser A G *et al*
Bosi E *see* Caforio A *et al*
Bottazzo G F *see* Caforio A *et al*
Boven v van *see* Van Boven V *et al*
Bowes R J (& Oakley G D G, Fleming J S, Cumberland D C) Early clinical experience with a laser wire for percutaneous angioplasty of chronically occluded coronary arteries 438 *P*
Bowker T *see* Davies S *et al*
Bowles N E *see* Archard L C *et al*
Boyd E *see* Rosenthal E *et al*
Boys R J *see* Robson S C *et al*
Bray C L *see* Molajo A O *et al*
Brembilla-Perrot B (& de la Chaise A T, Pichené M, Aliot E, Cherrier F, Pernot C) Isoprenaline as an aid to the induction of catecholamine dependent supraventricular tachycardias during programmed stimulation 348
Brender D *see* Smith R *et al*
Bresnahan D R *see* Bell M R *et al*
Bridges A *see* McMurray J *et al*
Brigden G *see* DasGupta P *et al*
Bristow J D *see* Conway M *et al*
British Cardiac Society autumn meeting, London, 22 to 24 November 1988, proceedings, 71
British Cardiac Society 68th Annual General Meeting, Oxford, 6 and 7 April 1989, proceedings, 435
Britton K *see* Levy R D *et al*
Broadhurst P (& Cashman P, DasGupta P, Lahiri A, Raftery E B) Comprehensive validation of the Cardioscint: a system for continuous monitoring of left ventricular function 465 *P*
— *see also* Lahiri A *et al*
Brook S *see* Gehani A A *et al*
Brooks S G (& Hamilton J R L, Dickinson D, Wilson N, Walker D R) Sinus venosus atrial septal defect: investigation and repair 89 *P*
Brown A M *see* Higham P D *et al*
Brown M J *see* Hall J A *et al*
Bryan A J (& Angelini G D, Williams H M J, Newby A C) Distension during surgical preparation reduces short term patency in a pig model of arteriovenous bypass grafting 464 *P*
— *see also* Angelini G D *et al*
Buchalter M B (& Weiss J L, Rogers W J, Zerhouni E A, Weisfeldt M L, Shapiro E P) Human left ventricular twist: measurement by magnetic resonance tagging 112 *P*
Buckels J *see* O'Kane H *et al*
Bucknall C (& Sulke N, Karani S, Sowton E) Initiation and termination windows in tachycardia: reproducible in the long term? 468 *P*
— *see also* Henderson R A *et al*
Bucknall S *see* Sulke N *et al*
Bull *see* Kilner P J *et al*
  Sullivan I D *et al*
Bull T *see* Keogh B E *et al*
Bullock R E *see* Peart I *et al*
Burke E (& McAleer B, McElhinney K, Ruane B, Williams J R, Varma M P S) Comparative one year mortality in patients treated with thrombolytic treatment at home and in the coronary care unit 72 *P*
— — — — — — Thrombolytic treatment in cardiogenic shock 88 *P*
Burns J M A (& Hogg K J, Hillis W S, Dunn F G) Endocarditis in intravenous drug abusers with staphylococcal septicaemia 356
— — Rae A P, Hillis W S, Dunn F G) Impact of a policy of direct admission to a coronary care unit on use of thrombolytic treatment 322
Burrell C J (& Blake D R) Reactive oxygen metabolites and the human myocardium: editorial 4

— (& Kitney R I, Straughan K, McDonald A H, Rothman M T) Intravascular three dimensional imaging of arteries: a novel ultrasound system 476 *P*
— *see also* Nouriel H *et al*
Skehan J D *et al*
Bush A *see* Carvalho J *et al*
Busst C *see* Carvalho J *et al*
Butrous G S (& Kaye G, Camm A J) Autonomic regulation of pre-excitation induced by respiration 473 *P*
— *see also* Garratt C J *et al*
Byrne P J *see* Robertson M A *et al*

Caforio A (& McKenna W J, Bonifacio E, Frenneaux M P, Bosi E, Bottazzo G F) Novel cardiac specific circulating autoantibodies in dilated cardiomyopathy 73 *P*
— — — Wagner R, Gill R, Bosi E, Bottazzo G F) Circulating autoantibodies against "myoendocrine" cells in patients with autoimmune polyendocrinopathy and systemic hypertension 457 *P*
Caforio A L P *see* Frenneaux M P *et al*
Caidahl K *see* Blomstrom-Lundqvist C *et al*
Campbell N P S *see* Flannery D J *et al*
McNeill A J *et al*
Campbell R W F *see* Dougeni-Christacou V *et al*
Camm A J *see* Butrous G S *et al*
Cripps T *et al*
de Belder M A *et al*
Farrell T *et al*
Garrett C J *et al*
Griffith M J *et al*
Leech G *et al*
Mehta D *et al*
Paul V E *et al*
Wafa S S *et al*
Canning G P *see* Northcote R J *et al*
Cant J *see* Baig M W *et al*
Capone R J *see* Boden W E *et al*
Cardinal R *see* Shenasa M *et al*
Carey C M *see* Skehan J D *et al*
Carvalho J (& Busst C, Bush A, Lincoln C R, Rigby M L, Shinebourne E A) Mustard's operation long term haemodynamics in symptom free children and balloon dilatation for systemic venous obstruction 90 *P*
Carvalho J S (& Rigby M L, Shinebourne E A, Anderson R H) Cross sectional echocardiography for recognition of ventricular topology in atrioventricular septal defect 285
Cashman P *see* Broadhurst P *et al*
Lahiri A *et al*
Caunt J *see* Lahiri A *et al*
Chaise A T de la *see* de la Chaise A T
Chakrabarty S (& Thomas P, Williams T, Sheridan D J) Influence of platelets on extent of myocardial infarction during coronary artery occlusion 78 *P*
Chambers J B (& Sampson M J, Springings D C, Jackson G) QT prolongation in diabetic autonomic neuropathy 97 *P*
— *see also* Monaghan M J *et al*
Sprigings D C *et al*
Chan K C *see* Clark D J *et al*
Chan-wah-hak N S *see* Metcalfe M J *et al*
Chen Z (& Collins R, Peto R, MacMahon S, Li W) The relations of serum cholesterol, blood pressure, and smoking habit to coronary heart disease in a population with low mean concentrations of serum cholesterol 460 *P*
Cherrier F *see* Brembilla-Perrot B *et al*
Chesebro J H *see* Penny W J *et al*
Chester A H *see* Dashwood M R *et al*
Child A H *see* Henney A M *et al*
Chopra M *see* McMurray J *et al*
Chow S *see* Hunt A C *et al*
Chow W H *see* Morgan J M *et al*
Christacou V Dougeni- *see* Dougeni-Christacou V
Christensen N J *see* Kelbæk H *et al*
Christie J *see* Cunningham D *et al*
Findlay I N *et al*
Clague J C *see* Morgan J M *et al*
Clark D J (& Chan K C, Gibbs J L) Propranolol induced bradycardia in tetralogy of Fallot: case report 378
Clayton-Jones D G *see* Pattison C W *et al*
Cleland J *see* O'Kane H *et al*
Cleland J F (& Sharabani R, Shahi M, Goldin R D, Foale R A) An immunological marker for alcohol related myocardial disease 113 *P*
Cobbe S M *see* Al-Riyami A *et al*
Hicks M & Cobbe CM
Pye M *et al*
Rankin A C *et al*
Cochrane T *see* Sprigings D C *et al*
Codd M B (& Sugrue D D, Gersh B J, Melton L J) Epidemiological features of the idiopathic cardiomyopathies a population based study 80 *P*
— *see also* Sugrue D D *et al*
Coghlan J G (& Madden B, Norell M S, Ilsley C, Mitchell A G) The influence of pacing rate on QT shortening with exercise 469 *P*
Colchester A F C *see* de Belder M A *et al*
Nevin M *et al*
Coleman E N *see* Houston A B *et al*
Coles G A *see* Lewis N P *et al*
Collins R (& Peto R, Sleight P for the ISIS Collaboration Group) ISIS-2. a large randomised trial of intravenous streptokinase and oral aspirin in acute myocardial infarction 71 *P*
— *see also* Chen Z *et al*
MacMahon S *et al*
Colvin P *see* Withington P S *et al*
Conroy R *see* O'Sullivan J J *et al*
Conway M (& Bristow J D, Blackledge M J, Rajagopalan B, Radda G K) Non-invasive measurement of phosphorus metabolism in the human heart during exercise by phosphorus-31 magnetic resonance spectroscopy 104 *P*
— *see also* Arnolda L *et al*
Conway M A (& Soper N, Shepstone B, Ledingham J G G, Sleight P) Exercise renography in patients with heart failure 80 *P*
Conway N *see* Smyllie J *et al*
Cook D G (& Shaper A G) Breathlessness, lung function, and risk of heart attack 122 *P*
— — Using the Rose angina questionnaire 114 *P*
— *see also* Whincup P H *et al*
Cooper I C (& Fry C H, Webb-Peploe M M) Myocardial hypertrophy and mechanical restitution in isolated human myocardium 112 *P*
— *see also* Katritsis D *et al*
Cooper S G *see* Sullivan I D *et al*
Correction 484
Counihan P J (& Frenneaux M P, O'Donoghue A, Webb D, McKenna W J) Abnormal peripheral vascular response in hypertrophic cardiomyopathy in relation to clinical and prognostic features 456 *P*
— *see also* Frenneaux M P *et al*
Court D S *see* Gershlick A H *et al*
Court D Syndercombe- *see* Syndercombe-Court D
Cowan J C *see* Baig M W *et al*
Cowley M L *see* Skehan J D *et al*
Cox A *see* Banner N R *et al*
Craig M *see* Finley J P *et al*
Crake T *see* Nadazdin A *et al*
Crawley J *see* Lahiri A *et al*
Crea F (& Pupita G, Galassi A R, El-Tamimi H, Kaski J C, Davies G, Maseri A) Adenosine and angina pectoris 455 *P*
— *see also* Kaski J C *et al*
Keogh B E *et al*
Pupita G *et al*

Creamer J E (& Edwards J D, Nightingale P) Monitoring oxygen transport in cardiogenic shock 445 *P*
Crean P *see* Black F *et al*
Cripps T (& Camm A J, Ward D E) Comparative value of clinical and electrophysiological variables in the prediction of arrhythmic events after myocardial infarction 83 *P*
— (& Frenneaux M, Camm A J, McKenna W J) Prediction of life threatening arrhythmias in hypertrophic cardiomyopathy using high gain, signal averaged electrocardiography 124 *P*
— *see also* Farrell T *et al*
Cripps T C *see* Farrell T G *et al*
Croal S *see* McKeown P *et al*
McKeown P P *et al*
Crombie I K (& Kenicer M B, Smith W C S, Tunstall-Pedoe H D) Unemployment, socioenvironmental factors, and coronary heart disease in Scotland 172
Crossman D C (& Larkin S W, Dashwood M, Davies G J, Yacoub M, Maseri A) Atherosclerotic human coronary vessels preserve a dilator response to substance P in vivo 455 *P*
Crowther A *see* Katritsis D *et al*
Cumberland D C *see* Bowes R J *et al*
Cumming D *see* Pattison C W *et al*
Cunningham D (& Kennedy J, Rowland E, Christie J, Rickards A) One hundred and thirty-three cases of spontaneous atrial flutter. electrophysiological characteristics and factors affecting successful conversion 123 *P*
Cunningham S R *see* Dalzell G W N *et al*
McNewill A J *et al*
Currie P (& Saltissi S) Ambulatory ST segment deviation after acute myocardial infarction: implications for exercise ischaemia and left ventricular function 454 *P*
Curry P *see* Rosenthal E *et al*
Curry P V L *see* Najm Y C *et al*
Priestley K *et al*
Priestley K A *et al*
Rosenthal E *et al*

Daele M van *see* van Daele M
Daele M E R M van *see* van Daele M E R M
Dahan S *see* Taha T H *et al*
Dalzell G W N (& Cunningham S R, Anderson J, Adgey A A J) Initial experience with a microprocessor controlled current based defibrillator 502
— *see also* Dickey W A *et al*
McKeown P P *et al*
McNeill A J *et al*
Dambrink J-H E *see* Parameshwar J *et al*
Daniel W *see* Sutherland G R *et al*
Dargie H *see* Dominiczak A *et al*
McAlpine H *et al*
Polonia J J *et al*
Dargie H J *see* Findlay I N *et al*
Northridge D B *et al*
Das S K *see* Stewart R A *et al*
Dasgupta P (& Brigden G, Ramhamdany E, Lahiri A, Baird I, Raftery E B) Improvement of subclinical left ventricular dysfunction on obese subjects after weight loss 101 *P*
— *see also* Broadhurst P *et al*
Dashwood M *see* Crossman D C *et al*
Dashwood M R (& Chester A H, Sykes R M, Yacoub M H) Autoradiographic localisation of (125$_{I}$) endothelin binding sites in human coronary artery· changes in ischaemic heart disease 440 *P*
Davies D W (& Barin E S, Wong C Y, Levy R D, Nathan A W) Are haemodynamic changes during ventricular tachycardia useful in treatment? 466 *P*
— *see also* Ratnatunga C P *et al*
Davies E *see* Flapan A D *et al*
Davies G *see* Crea F *et al*
Davies G J *see* Andreotti F *et al*
Crossman D C *et al*
El-Taminni H *et al*
Keogh B E *et al*
Khan M I *et al*
Davies M J Successful and unsuccessful coronary thrombolysis: editorial 381
— *see also* de Belder M A *et al*
Keogh B E *et al*
McKenna W J *et al*
Mehta D *et al*
Davies M K *see* Fox J P *et al*
Shaw T R D *et al*
Davies S (& Gardener J, Bowker T, Timmis A, Balcon R) Haemodynamic assessment of mitral stenosis in the presence of atrial fibrillation 116 *P*
— (& Keegan J, Wilkinson P, Bailey J, Timmis A, Wedzicha J, Rudd R) Decreased pulmonary microvascular permeability in patients with severe mitral stenosis 91 *P*
— (& Marchant B, Lyons J, Timmis A, Rothman M, Layton C, Balcon R) Coronary lesion morphology in patients with acute myocardial infarction treated with streptokinase 72 *P*
— (& Underwood S, Wickens D, Feneck R, Walesby R, Dormandy T) Comparative lack of free radical generation by the myocardium during cardiac surgery 78 *P*
— *see also* Norell M S *et al*
Davies S W (& Bailey J, Keegan J, Lipkin D P, Balcon R, Rudd R) Pulmonary capillary permeability in chronic left heart failure 477 *P*
— (& Emery T M, Watling M I L, Lipkin D P) Critical level of exercise capacity determines the hyperventilation response to exercise in chronic heart failure 436 *P*
— — — (Macfarlane D, Shaper A G, Lipkin D P) Fitness and coronary risk factors 444 *P*
— (& Greig C, Jordan S L, Grieve D W, Lipkin D P) Inefficient gait contributes to reduced exercise capacity in chronic heart failure 437 *P*
— (& Jordan S L, Lipkin D P) Dyspnoea on exercise in chronic heart failure is dissociated from hyperventilation 443 *P*
— (& Marchant B, Lyons J P, Timmis A D, Layton C, Rothman M T, Balcon R) Coronary lesions after thrombolysis: irregularity predicts need for urgent intervention 452 *P*
— (& Wedzicha J A, John L M E, Balcon R, Lipkin D P) Hypoxia, myocardial ischaemia, and arrhythmias during sleep in chronic heart failure 458 *P*
Dawkins K *see* Smyllie J *et al*
Dawson J R (& Gibson D G) Left ventricular filling and early diastolic function at rest and during angina in patients with coronary artery disease 248
Deanfield J E *see* Franklin R C G *et al*
Sullivan I D *et al*
de Belder M *see* Khan B *et al*
de Belder M A (& Hawkes D J, Norbury R N, Colchester A F C, Davies M J, Camm A J) Densitometric angiographic assessment of normal and diseased coronary arteries validation of technique 115 *P*
— (& Leech G, Camm A J) Transoesophageal echocardiography· method of choice to visualise left atrial pathology 478 *P*
— (& Skehan J D, Pumphrey C W, Evans S J W, Rothman M T, Mills P G) Collateral vessels after infarction. association with left ventricular damage and coronary disease, and influence on exercise testing and clinical outcome 83 *P*
— *see also* Leech G *et al*
Skehan J D *et al*
de Feyter P J *see* Beatt K J *et al*
de Giovanni J V *see* Salmon A P *et al*
de la Chaise A T *see* Brembilla-Perrot B *et al*
Deleval M R *see* Kilner P J *et al*
de Medina E O Robles *see* Robles de Medina E O
de Mey C (& Belz G G) Pitfalls and limitations in the use of impedance cardiography correspondence 128
der Lippe G von *see* von der Lippe G

Deverall P *see* Rosenthal E *et al*
Deverall P B *see* Ladusans E J *et al*
Parsons J M *et al*
Devereux R B *see* Henney A M *et al*
Devlin B D *see* Flannery D J *et al*
Dhalla N *see* Aranki S *et al*
Dickey W (& Khan M M, Adgey A A J) Electrophysiological study of survivors outside hospital from ventricular arrhythmias unassociated with acute myocardial infarction 118 *P*
Dickey W A (& Dalzell G W N, Magee W H, Beggs O, Bailey A, Anderson J, Adgey A A J) Accuracy of a semiautomatic defibrillator during cardiac arrests 98 *P*
Dickie S *see* McKenna W J *et al*
Dickinson D *see* Brooks S G *et al*
Dickinson D F *see* Qureshi S A *et al*
Dilly S G *see* Northridge D B *et al*
Diltiazem Reinfarction Study Research Group *see* Boden W E *et al*
Doherty J D Electrophysiological changes in an animal model of experimental chronic cardiac failure 104 *P*
Doig W B *see* Houston A B *et al*
Dolecki M *see* Arnolda L *et al*
Dominiczak A (& Morton J, Dargie H, Semple P) Association between blood pressure, left ventricular mass and free cytosolic calcium in primary hyperparathyroidism and essential hypertension 104 *P*
Dormandy T *see* Davies S *et al*
Dougeni-Christacou V (& Dougenis D, Tai Y T, McComb J, Campbell R W F) Hospital mortality of ventricular tachycardia and fibrillation 125 *P*
Dougenis D *see* Dougeni-Christacou V *et al*
Dubuc M *see* Shenasa M *et al*
Dunn F G *see* Burns J M A *et al*
Hogg K J *et al*
Dunn M J *see* Pattison C W *et al*
Dyke L *see* Levy R D *et al*
Dyke L J *see* Wiseman M N *et al*
Dymond D S *see* Levy R D *et al*
Wiseman M N *et al*

Edmondson S J *see* Ratnatunga C P *et al*
Edwards C R W *see* Flapan A D *et al*
Edwards D *see* Virginia M *et al*
Edwards J D *see* Creamer J E *et al*
Elborn J S (& Stanford C F, Nicholls D P) Effect of flosequinan on exercise capacity and symptoms in severe heart failure 331
Ell P J *see* Mittal R B *et al*
Underwood S R *et al*
Elstob J *see* Levy R D *et al*
El-Tamimi H (& Hackett D, Davies G J, Larkin S, Maseri A) Can exercise testing predict restenosis after coronary angioplasty? 95 *P*
— *see also* Crea F *et al*
Emanuel R W *see* Underwood S R *et al*
Emery T M *see* Davies S W *et al*
Engberding R *see* Sutherland G R *et al*
Erbel R *see* Sutherland G R *et al*
Escanade J *see* Hunt A C *et al*
Espejo R *see* Wharton J *et al*
Essop A R *see* Shaw T R D *et al*
Evans B, William Evans; Obituary 68
Evans S J W *see* de Belder M A *et al*

Falk E *see* Andersen H R *et al*
Farrell T (& Cripps T, Camm A J, Ward D E) Prognostic value of heart rate variability after myocardial infarction 121 *P*
Farrell T G (& Cripps T C, Paul V, Camm A J) Baroreceptor sensitivity in patients after infarction correlation with electrophysiological studies 472 *P*
Faxon D P *see* Glazier J J *et al*
Feith F *see* Rees M R *et al*
Feneck R *see* Davies S *et al*
Feyter P J de *see* de Feyter P J
Findlay I N (& Northridge D, Wilson J T, Henderson E, Christie J, Dargie H J) Non-invasive measurement of cardiac output during acute myocardial infarction by electrical bioimpedance cardiography 444 *P*
— *see also* Northridge D B *et al*
Finley J P (& Nugent S T, Hellenbrand W, Craig M, Gillis D A) Sinus arrhythmias in children with atrial septal defect: an analysis of heart rate variability before and after surgical repair 280
Firmin D N *see* Mohiaddin R H *et al*
Fisch C *see* Meijler F L & Fisch C
Fitzgerald M *see* Aravot D *et al*
Fitzpatrick A (& Theodorakis G, Travill C, Sutton R) Incidence of malignant vasovagal syndrome in 332 syncopal patients: results of cardiac pacing 97 *P*
Flannery D J (& Devlin B D, Campbell N P S) Pulsed Doppler assessment of left ventricular diastolic function in acute myocardial infarction 466 *P*
— *see also* McNeill A J *et al*
Flapan A D (& Davies E, Williams B C, Edwards C R W, Shaw T R D) Captopril does not potentiate the action of loop diuretics in patients with cardiac failure 87 *P*
Fleming J S *see* Bowes R J *et al*
Foale R A *see* Cleland J F *et al*
Keogh B E *et al*
Nadazdin A *et al*
Foley B *see* Black F *et al*
Forfar J C *see* McCance A J & Forfar J C
Forsyth A *see* Bergman G *et al*
Fox J P (& Beattie J M, Salih M S, Davies M K, Littler W A, Murray R G) Functional and angiographic comparison of symptomatic and silent ischaemia 436 *P*
— (& Murray R G, Beattie J M, Salih M, Davies M K, Littler W A) Characteristics and prognosis of non-Q wave myocardial infarction 122 *P*
Fox K *see* Mulcahy D *et al*
Fox K A A (& Robison A K, Bergmann S R) Inhibition of coronary thrombosis with low dose tissue plasminogen activator (t-PA): the potential for modifications of endogenous t-PA activity 73 *P*
— *see also* Lewis N P *et al*
Fragomeni L S *see* Bonser R S *et al*
Franciosi J *see* Ladusans E J *et al*
Franklin R C G (& Sullivan I D, Anderson R H, Deanfield J E) Is pulmonary artery banding obsolete for double inlet ventricle and tricuspid atresia? 479 *P*
Franklyn J A *see* Gammage M D *et al*
Heagerty A M *et al*
Fraser A G (& van Herwerden L, van Daele M E R M, Bos E, Roelandt J R T C, Sutherland G R) The relative values of intraoperative epicardial and transoesophageal echocardiography in mitral valve repair 451 *P*
— *see also* Mulligan I P *et al*
Freedom R M *see* Ino T *et al*
Koike K *et al*
Leung M P *et al*
Freeke C *see* Archard L C *et al*
French W J *see* Haskell R J & French W J
Frenneaux M *see* Cripps T *et al*
Karatasakis G *et al*
Frenneaux M P (& Counihan P J, Webb D, McKenna W J) Evidence for an abnormal vasodilator response in hypertrophic cardiomyopathy 74 *P*
— (& Lowe T, Lipkin D P, McKenna W J) Objective assessment of exercise capacity in hypertrophic cardiomyopathy: association with clinical and prognostic features 75 *P*
— (& Porter A, Caforio A L P, Odawara H, Counihan P J, McKenna W J) Rise in left atrial pressure does not limit exercise capacity in patients with hypertrophic cardiomyopathy 118 *P*
— *see also* Alfonso F *et al*
Caforio A *et al*
Counihan P J *et al*

Fry C H *see* Cooper I C *et al*
Fujiwara H *see* Onodera T *et al*
Furniss S S *see* Robson S C *et al*
Fuster V *see* Penny W J *et al*

Galassi A R *see* Crea F *et al*
Pupita *et al*
Galvin I *see* O'Kane H *et al*
Gammage M D (& Franklyn J A, Green N K, Sheppard M C) Myocardial proto-oncogene expression and effects of thyroid state 441 *P*
— *see also* Heagerty A M *et al*
Gardener J *see* Davies S *et al*
Garratt C J (& Antoniou A, Griffith M J, Ward D E, Camm A J) Unmasking of latent pre-excitation· efficacy of adenosine and vagal manoeuvres in sinus rhythm 467 *P*
— (& Griffith M J, Butrous G S, Ward D E, Camm A J) Pre-excitation induced by exercise: association with anteroseptal accessory atrioventricular connections that are sensitive to adenosine and verapamil 475 *P*
— *see* Paul V E *et al*
Gehani A A (& Latif A B, Ashley S, Brook S, Ball S G, Rees M R) Dynamic angioplasty in normal and abnormal coronary arteries 85 *P*
—*see also* Rees M R *et al*
Gerlis L M (& Ho S Y) Anomalous subaortic position of the brachiocephalic (innominate) vein: a review of published reports and report of three new cases 540
Gersh B J *see* Codd M B *et al*
Sugrue D D *et al*
Gershlick A *see* Balcon R *et al*
Gershlick A H (& Court D S, Timmis A, Rothman M, Layton C, Balcon R) Transcardiac changes in platelet function before and after angioplasty 83 *P*
— (& Syndercombe-Court A D, Timmis A D, Rothman M T, Layton C, Balcon R) Can epoprostenol (prostacyclin) infusion during coronary angioplasty prevent adverse changes in platelet function? 461 *P*
Geuskens R *see* Beatt K J *et al*
Sutherland G R *et al*
Gewillig M *see* Kilner P J *et al*
Ghosh P *see* Nihoyannopoulos P *et al*
Gibbs J L *see* Clark D J *et al*
Gibson D *see* Vancheri F & Gibson D
Gibson D G *see* Dawson J R & Gibson D G
Luke R A *et al*
Gibson R S *see* Boden W E *et al*
Gill R *see* Caforio A *et al*
Gillbe C E *see* Luke R A *et al*
Gilligan D *see* Moore D P *et al*
Gillis D A *see* Finley J P *et al*
Gilmour S *see* Mehta D *et al*
Giovanni J V de *see* De Giovanni J V
Gladstone D *see* O'Kane H *et al*
Glazier J J (& Varrichione T R, Ruocco N A, Jacobs A, Ryan T J, Faxon D P) Importance of precedural factors in the development of recurrent restenosis after coronary balloon angioplasty 94 *P*
— — (Ryan T J, Ruocco N A, Jacobs A, Faxon D P) Management and outcome of patients with recurrent restenosis after coronary balloon angioplasty 95 *P*
— — — — — — — Outcome in patients with recurrent restenosis after percutaneous transluminal balloon angioplasty 485
Godtfredsen J *see* Kelbæk H *et al*
Goldin R D *see* Cleland J F *et al*
Goldspink G *see* Pattison C W *et al*
Gomez P (& Nihoyannopoulos P, Joshi J, Loizou S, Walport M, Oakley C) Cardiac abnormalities in systemic lupus erythematosus: association with raised cardiolipin antibodies 80 *P*
Goodwin J F *see* McKenna W J *et al*
Goudevenos J (& Been M, Williams D) Serial angiographic findings during the development of a saccular aneurysm of the coronary artery in association with unstable angina: case report 372
Goy J-J (& Kappenberger L, Turina M) Wolff-Parkinson-White syndrome after transplantation of the heart: case report 368
Graham T R *see* Withington P S *et al*
Grahame-Smith D G *see* Pugh S E *et al*
Gray H H *see* Morgan J M *et al*
Green N K *see* Gammage M D *et al*
Heagerty A M *et al*
Greenberg G *see* Thompson S G *et al*
Greig C *see* Davies S W *et al*
Grieve D W *see* Davies S W *et al*
Griffin S (& Pugsley W, Treasure T) Middle cerebral artery microembolism: a comparison of bubble oxygenator with arterial line filter and membrane oxygenator alone 449 *P*
Griffith M J (& Linker N J, Micklewright J, Ward D E, Camm A J) Simplification of the diagnosis of broad complex tachycardia by multivariate analysis 475 *P*
— (& Linker N J, Ward D E, Camm A J) Comparative efficacy and safety of adenosine, lignocaine, disopyramide, flecainide, and sotalol in the determination of ventricular tachycardia 123 *P*
—— *see also* Garrett C J *et al*
Grimm J *see* Jenni R *et al*
Gussenhoven E J *see* Sutherland G R *et al*
Gussenhoven W J *see* Sutherland G R *et al*
Taams M A *et al*
Guz A *see* Banner N R *et al*

Hackett D *see* El-Tamimi H *et al*
Kaski J C *et al*
Khan M I *et al*
Hak N S Chan-Wah- *see* Chan-Wah-Hak NS
Hall A *see* Peart I *et al*
Hall J A (& Petch M C, Brown M J) Intracoronary injections of salbutamol show the presence of beta$_2$ adrenoreceptor mediated activity in the human heart 108 *P*
Hall R J C *see* Ikram S *et al*
Peart I *et al*
Halson P *see* Kaski J C *et al*
Khan M I *et al*
Hamilton J *see* Andreotti F *et al*
Hamilton J R L *see* Brooks S G *et al*
Hamilton R D *see* Banner N R *et al*
Hampton J R *see* Wilcox R G *et al*
Handler C E (& Livesey S, Lawton P A) Coronary ostial stenosis after radiotherapy: angioplasty or coronary artery surgery? case report 208
Hanrath P *see* Sutherland G R *et al*
Harrison M *see* Pugsley W *et al*
Venn G E *et al*
Hart H *see* White H D *et al*
Haskell R J (& French W J) Physiological importance of different atrioventricular intervals to improved exercise performance in patients with dual chamber pacemakers 46
Hatle L *see* Samstad S O *et al*
Hauer R N W (& Robles de Medina E O, Kuijer P J, Westerhof P W) Electrode catheter ablation for ventricular tachycardia: efficacy of a single cathodal shock 38
Hawkes D J *see* de Belder M A *et al*
Haworth S G *see* Hislop A A *et al*
Hayward R *see* Taggart P *et al*
Hazekamp M *see* Angelini G *et al*
Heads A *see* Robson S C *et al*
Heagerty A M (& Green N K, Maciver D H, Franklyn J A, Gammage M D) Inositol phosphate production and proto-oncogene expression in left ventricle after the induction of coarctation hypertension in the rat 440 *P*
Hegrenaes L *see* Samstad S O *et al*
Hellenbrand W *see* Finley JP *et al*
Henderson A H *see* Mulligan I P *et al*

HENDERSON E *see* Findlay I N *et al*
HENDERSON R A (& Karani S, Bucknall C, Sowton E) Long term clinical results after successful coronary angioplasty in multivessel disease 438 *P*
—— (& Karani S, Pipilis A, Bucknall C, Timmis A D, Sowton E) Long term clinical follow up after coronary angioplasty for single vessel disease 95 *P*
HENNEY AM (& Tsipouras P, Schwartz R C, Child A H, Devereux R B, Leech G J) Genetic evidence that mutations in the COL1A1, COL1A2, CO13A1, or COL5A2 collagen genes are not responsible for mitral valve prolapse 292
HERAS M *see* Penny W J *et al*
HERLITZ J (& Hjalmarson Å, Waagstein F) Treatment of pain in acute myocardial infarction review 9
HERWERDEN L VAN *see* van Herwerden L
HESS J *see* Sutherland G R *et al*
HICKS M (& Cobbe S M) Effects of sotalol on the rate of accumulation of extracellular potassium in ischaemic myocardium 442 *P*
HIGHAM P D (& Bleasdale C, Brown A M, Saltissi S, Jackson M J, Hind C R K) Circulating concentrations of free radicals in patients with myocardial infarction 454 *P*
HILLIS W S *see* Burns J M A *et al*
Hogg K J *et al*
HILTON C *see* Ikram S *et al*
HIND C R K *see* Higham P D *et al*
HIRZEL H O *see* Jenni R *et al*
HISLOP A A (& Odom N, McGregor C G A, Haworth S G) Growth potential of the immature transplanted rat lung 82 *P*
HJALMARSON Å *see* Herlitz J *et al*
HO S Y *see* Barin E S *et al*
Gerlis L M and Ho S Y
HODSMAN G P *see* Phillips P A *et al*
HOGG K J (& Lees K R, Hornung R S, Howie C A, Dunn F G, Hillis W S) Electrocardiographic evidence of myocardial salvage after thrombolysis in acute myocardial infarction 489
— *see also* Burns J M A *et al*
HOLDER R *see* Salmon A P *et al*
HOLMES D R *see* Bell M R *et al*
Penny W J *et al*
HOLMES K M *see* Robson R H *et al*
HONG R *see* Bhandari A K *et al*
HONGO M *see* Kinoshita O *et al*
HOPKINS N *see* Andreotti F *et al*
HORNUNG R S *see* Hogg K J *et al*
HOROWITZ J *see* Phillips P A *et al*
HOUSTON A B (& Lim M K, Coleman E N, Doig W B, Reid J M) Impact of colour Doppler flow mapping on the assessment of congenital heart disease 120 *P*
HOWIE C A *see* Hogg K J *et al*
HUDSON N *see* Pappageorgio G L *et al*
HUGHES L (& Lahiri A, Raftery E B) Coronary disease in Asians associated with high insulin and C-peptide concentration 445 *P*
HUGHES L O (& Raval U, Raftery E B) Early coronary atherogenesis and myocardial infarction in Asians: a problem of glucose metabolism 78 *P*
HUNT A C (& Escanade J, Chow S, Beattie J, Shiu M F) Complication rates of single and multiple vessel coronary angioplasty in multivessel coronary artery disease 440 *P*
HUNT A E *see* Seth A *et al*
HUNT A G (& Seth A, Perry R A, Lowry P, Shiu M F) Use of Doppler echocardiography in determination of left ventricular dP/dt max 116 *P*
HUNTER D *see* John R M *et al*
HUNTER S *see* Qureshi S A *et al*
Sreeram N *et al*
Sullivan I D *et al*
Wren C & Hunter S
HUTTON I *see* McGhie I *et al*
Pye M *et al*
Tweddel A *et al*
Tweddel A C *et al*
HUYSMANS H *see* Angelini G *et al*

IKEDA S-I *see* Kinoshita O *et al*
IKRAM S (& Maire R, Lewis P A, Odemuyiwa O, Lo S V, Hilton C, Hall R J C) Tricuspid regurgitation and pulmonary artery pressure five years after implantation of mitral bioprostheses 450 *P*
ILSLEY C *see* Coghlan J G *et al*
INGRAM D *see* Ambepityia G *et al*
INNES J A *see* Banner N R *et al*
INO T (& Benson L N, Mikailian H, Freedom R M, Rowe R D) Determination of left ventricular volumes by Simpson's rule in infants and children with congenital heart disease 182
INOUE H *see* Toda I *et al*
ISHIDA M *see* Onodera T *et al*

JAARSMA W *see* Sutherland G R *et al*
JACKSON G *see* Akhras F & Jackson G
Bergman G *et al*
Chambers J B *et al*
Jewitt D *et al*
Monaghan M J *et al*
Springings D C *et al*
Wordsworth P *et al*
JACKSON M J *see* Higham P D *et al*
JACOBS A *see* Glazier J J *et al*
JACOBS A K *see* Glazier J J *et al*
JAIN D (& Lahiri A, Raval U, Smith T, Raftery E B) Do reciprocal electrocardiographic changes in acute Q wave myocardial infarction represent additional ischaemia or necrosis? 471 *P*
JAMES M A Role of wall stress in the pathogenesis of ventricular arrhythmia 105 *P*
JAMIESON S W *see* Bonser R S *et al*
JARRIT P H *see* Mittal R B *et al*
JENNI R (& Ritter M, Viele A, Hirzel H O, Schmid E R, Grimm J, Turina M) Determination of the ratio of pulmonary blood flow to systemic blood flow by derivation of amplitude weighted mean velocity from continuous wave Doppler spectra 167
JENNINGS K *see* Metcalfe M J *et al*
JENSSEN G *see* Wilcox R G *et al*
JEWITT D (& Meany B, Thomas S, Monaghan M, Jackson G) Balloon dilatation of the mitral valve by double and single balloon techniques 91 *P*
JEWITT D E *see* Bergman G *et al*
Monaghan M J *et al*
JOHN L M E *see* Davies S W *et al*
JOHN R *see* Mittal R B *et al*
Taggart P *et al*
JOHN R M (& Hunter D, Swanton R H) Cardiac abnormalities in patients with type IV mucopolysaccharidosis Morquio syndrome 450 *P*
—(& Pugsley W, Treasure T, Sturridge M F, Swanton R H) Aortic root abscess complicating aortic valve endocarditis 93 *P*
JOHNSTON C I *see* Phillips P A *et al*
JONES D G CLAYTON *see* Clayton-Jones D G
JONES N B *see* Pappageorgio G L *et al*
JONES S *see* Till J A *et al*
JORDAN S L *see* Davies S W *et al*
JOSEPH S Correcting a block?: successful experience of a small British pacing centre: correspondence 212
JOSHI J *see* Gomez P *et al*
Kambouroglou D *et al*
Nihoyannopoulos P *et al*

KAHALY S MOHR- *see* Mohr-Kahaly S
KALTENBRUNNER W *see* Shenasa M *et al*
KAMBOUROGLOU D (& Joshi J, Nadazdin A, Karatasakis G, Smith P, Nihoyannopoulos P) What is normal function of an artificial

valve? A colour and continuous wave Doppler assessment 126 *P*
— *see* Nihoyannopoulos P *et al*
Kameda T *see* Toyama M *et al*
Kamp O *see* Beatt K J *et al*
Kappenberger L *see* Goy J-J *et al*
Karani S *see* Bucknall C *et al*
Henderson R A *et al*
Sulke N *et al*
Karatasakis G (& Nihoyannopoulos P, Frenneaux M, McKenna W J, Stewart R, Oakley C) Are Doppler diastolic indices associated with functional capacity in patients with hypertrophic cardiomyopathy? 100 *P*
— *see also* Kambouroglou D *et al*
Kaski J C (& Maseri A, Vejar M, Halson P, Crea F, Hackett D) Spontaneous coronary spasm in variant angina results from a local coronary hyperreactivity to a generalised constrictor stimulus 456 *P*
— *see also* Crea F *et al*
Pupita G *et al*
Katritsis D (& Lythall D A, Crowther A, Copper I C, Webb-Peploe M M) Comparison of visual estimation, measurement by hand held calipers, automated digital quantifications, for the assessment of results of percutaneous transluminal coronary angioplasty 85 *P*
— *see also* Smith L D R *et al*
Kawahara T *see* Toda I *et al*
Kawai C *see* Onodera T *et al*
Kawakubo K *see* Toda I *et al*
Kawamura A *see* Onodera T *et al*
Kaye G *see* Butrous G S *et al*
Kaye M P *see* Bonser R S *et al*
Keegan J *see* Davies S *et al*
Keegan J *see* Davies S W *et al*
Mulcahy D *et al*
Keenan D J M *see* Price C & Keenan D J M
Keeton B R *see* Balaji S *et al*
Kelbæk H (& Munck O, Christensen N J, Godtfredsen J) Central haemodynamic changes after a meal 506
Kelly C *see* Peart I *et al*
Kenicer M B *see* Crombie I K *et al*
Kennedy J *see* Cunningham D *et al*
Keogh B E (& Crea F, Bull T, Pashazadeh M, Blackie R A S, Foale R A, Davies G J, Kidner P H, Davies M J, Taylor K M) Laser thermal angioplasty· limitations in the coronary circulation 86 *P*
Kerr F Correcting a block?: successful experience of a small British pacing centre. correspondence reply 212
Khaghani A *see* Aranki S *et al*
Aravot D *et al*
Khan B (& de Belder M, Skehan J D, Mills P G) Comparison of silent ischaemia after infarction and in chronic stable angina. effect of diltiazem 471 *P*
— *see also* Nouriel H *et al*
Khan M I (& Hackett D R, McFadden E, Andreotti F, Halson P, Davies G J, Maseri A) Serial intravenous bolus injections of recombinant tissue type plasminogen activator are associated with rapid recanalisation in patients with acute myocardial infarction 453 *P*
Khan M M *see* Dickey W *et al*
McKeown P *et al*
McNeill A J *et al*
Kidner P H *see* Keogh B E *et al*
Kilner P J (& de Leval M R, Bull C, Gewillig M) In vitro flow studies to improve hydrodynamic design of Fontan reconstruction 89 *P*
Kinoshita O (& Hongo M, Yamada H, Misawa T, Kono J, Okubo S, Ikeda S-I) Impaired left ventricular diastolic filling in patients with familial amyloid polyneuropathy a pulsed Doppler echocardiographic study 198
Kirk C R (& Radley-Smith R, Yacoub M H) Late left ventricular function after anatomical correction of anomalous left coronary artery 110 *P*
Kirkham N (& Murrells T, Melcher D H, Morrison E A) Diagonal earlobe creases and fatal cardiovascular disease: a necropsy study 361
Kitney R I *see* Burrell C J *et al*
Kleiger R E *see* Boden W E *et al*
Klinger L *see* Pugsley W *et al*
Venn G E *et al*
Kluft C *see* Andreotti F *et al*
Knight C *see* MacMahon S *et al*
Koike K (& Musewe N N, Smallhorn J F, Freedom R M) Distinguishing between anomalous origin of the left coronary artery from the pulmonary trunk and dilated cardiomyopathy: role of echocardiographic measurement of the right coronary artery diameter 192
Kono J *see* Kinoshita O *et al*
Koolen J *see* Sutherland G R *et al*
Kopelman P G *see* Ambepitiya G *et al*
Kotlewski A *see* Bhandari A K *et al*
Krikler D M A 59 year perspective: *British Heart Journal:* jubilee editorial 1
— *see also* McKenna W J *et al*
Kuijer P J *see* Hauer R N W *et al*

La Chaise A T de *see* de la Chaise A T
Lab M J *see* Taggart P *et al*
Lachno D R *see* Banner N R *et al*
Lacroix D *see* Shenasa M *et al*
Ladusans E J (& Murdoch I, Franciosi J) Severe haemolysis after percutaneous closure of a ductus arteriosus (arterial duct). case report 548
— (& Parsons J M, Baker E J, Martin R, O'Brien B, Deverall P B, Tynan M, Radley-Smith R C, Yacoub M H) Total correction of the tetralogy of Fallot· assessment of survival 90 *P*
— — (Qureshi S A, Baker E J, Tynan M J) Results of percutaneous balloon dilatation for critical aortic stenosis in neonates with severe endocardial fibroelastosis 470 *P*
— *see also* Baker E J *et al*
Parsons J M *et al*
Qureshi S A *et al*
Lahiri A (& Cashman P, Broadhurst P, Crawley J, Caunt J, Raftery E B) Cardioscint: a new system for the continuous evaluation of left ventricular function 102 *P*
— *see also* Broadhurst P *et al*
Das Gupta P *et al*
Hughes L *et al*
Jain D *et al*
Laming P J *see* Underwood S R *et al*
Langenstein B *see* Sutherland G R *et al*
Larkin S *see* El-Tamimi H *et al*
Larkin S W *see* Crossman D C *et al*
Latif A B *see* Gehani A A *et al*
Lawton P A *see* Handler C E *et al*
Layton C *see* Balcon R *et al*
Davies S *et al*
Layton C *see* Davies S W *et al*
Gershlick A H *et al*
Leblanc A-R *see* Shenasa M *et al*
Leckie B *see* Polonia J J *et al*
Ledingham J *see* Arnolda L *et al*
Ledingham J G G *see* Conway M A *et al*
Ledingham S J M (& Yacoub M) Beneficial effect of adenosine during reperfusion after prolonged cardioplegic arrest 442 *P*
Leech G (& de Belder M A, Camm A J) Outpatient transoesophageal echocardiography technique, patient tolerance, and costs 479 *P*
— *see also* de Belder M A *et al*
Henney AM *et al*
Lees K R *see* Hogg K J *et al*
Leung M P (& Benson L N, Smallhorn J F, Williams W G, Trusler G A, Freedom R M) Abnormal cardiac signs after Fontan type of operation: indicators of residual and sequelae 52

Levy R D (& Elstob J, Wiseman M N, Solanki K, Sobnack R, Dyke L, Britton K, Dymond D S) Indium-111 labelled monoclonal antimyosin antibody for the detection of myocardial necrosis in subendocardial infarction and unstable angina 101 *P*
— *see also* Davies D W *et al*
Lewis C T *see* Withington P S *et al*
Lewis M J *see* Mulligan I P *et al*
Lewis N P (& Macdougall I C, Coles G A, Williams J D, Fox K A A) Increased exercise capacity and reversal of exercise induced myocardial ischaemia in haemodialysis patients treated with recombinant human erythropoietin 436 *P*
Lewis P A *see* Ikram S *et al*
Li W *see* Chen Z *et al*
Lim M K *see* Houston A B *et al*
Lincoln C *see* Musumeci F & Lincoln C
Lincoln C R *see* Carvalho J *et al*
Lindsay D *see* Mulcahy D *et al*
Linker N J *see* Griffith M J *et al*
Lipkin D P *see* Davies S W *et al*
Frenneaux M P *et al*
Lippe G von der *see* von der Lippe G
Littler W A *see* Fox J P *et al*
Shaw T R D *et al*
Tan L B *et al*
Liu J Y *see* Walker J M & Liu J Y
Livesey S *see* Handler C E *et al*
Lloyd M H *see* Banner N R *et al*
Lo E *see* Yousif H *et al*
Lo S V *see* Ikram S *et al*
Loizou S *see* Gomez P *et al*
Longmore D B *see* Mohiaddin R H *et al*
Underwood S R *et al*
Lowe T *see* Frenneaux M P *et al*
Lowry P *see* Hunt A G *et al*
Lui D *see* Mittal R B *et al*
Luijten H E *see* Beatt K J *et al*
Luke R A (& Gillbe C E, Bonser R S, Paneth M, Somerset D, Thomas J, Gibson D G) Effect of temperature on rate of left ventricular pressure fall in humans 426
Lundqvist C Blomstrom- *see* Blomström-Lundqvist C
Lyons J *see* Davies S *et al*
Lyons J P *see* Davies S W *et al*
Norell M S *et al*
Lythall D A *see* Katritsis D *et al*

McAleer B *see* Burke E *et al*
McAlpine H (& Polonia J, Morton J J, Rumley A, Dargie H) Neuroendocrine responses to captopril in acute heart failure after myocardial infarction 81 *P*
McAreavey D *see* Shaw T R D *et al*
McCance A J Cardiac sympathetic neural activity in ischaemic heart disease 105 *P*
—(& Forfar J C) Cardiac and whole body (^{3}H)noradrenaline kinetics in ischaemic heart disease contrast between unstable anginal syndromes and pacing induced ischaemia 238
— — Cardiac noradrenaline output during percutaneous transluminal coronary angioplasty 461 *P*
McComb J *see* Dougeni-Christacou V *et al*
McCredie M *see* Smith R *et al*
McDonald A H *see* Burrell C J *et al*
Skehan J D *et al*
MacDonald R *see* Ambepitiya G *et al*
MacDougall I C *see* Lewis N P *et al*
McElhinney K *see* Burke E *et al*
McFadden E *see* Khan M I *et al*
MacFarlane D *see* Davies S W *et al*
Whincup P H *et al*
Macfarlane P W *see* Al-Riyami A *et al*
McGhie I (& Tweddel A, Martin W, Hutton I) Right ventricular dysfunction enhances mortality after myocardial infarction 121 *P*
— *see also* Tweddel A *et al*
Tweddel A C *et al*
McGhie J *see* Sutherland G R *et al*
McGregor C *see* Robson S C *et al*
McGregor C G A *see* Hislop A A *et al*
Machado L *see* Virginia M *et al*
McIntosh N *see* Bhandari A K *et al*
MacIver D H *see* Heagerty A M *et al*
McKenna T *see* O'Sullivan J J *et al*
McKenna W J (& Adams K M, Poloniecki J D, Dickie S, Oakley C M, Krikler D M, Goodwin J F) Long term survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia 472 *P*
— (& Nihoyannopoulos P, Davies M J) Hypertrophic cardiomyopathy without hypertrophy a description of two families with premature cardiac death and myocardial disarray in the absence of increased muscle mass 75 *P*
— *see also* Alfonso F *et al*
Caforio A *et al*
Counihan P J *et al*
Cripps T *et al*
Frenneaux M P *et al*
Karatasakis G *et al*
Mehta D *et al*
Stewart R A *et al*
Wasa S S *et al*
McKeown P (& Croal S, Allen J D, Anderson J, Khan M M, Adgey A A J) Transoesophageal approach to defibrillation of ventricular fibrillation 468 *P*
McKeown P P (& Croal S, Dalzell G W N, Anderson J, Adgey A A J) Transoesophageal DC cardioversion 96 *P*
McLay J *see* McMurray J *et al*
MacMahon S (& Collins R, Knight C, Yusuf S, Peto R) Reduction in major morbidity and mortality by heparin in acute myocardial infarction 118 *P*
— *see also* Chen Z *et al*
McMurray J (& Chopra M, McLay J, Scott N, Bridges A, Belch J) Free radical activity in chronic heart failure and effect of captopril 457 *P*
McNeill A J (& Cunningham S R, Flannery D J, Dalzell G W N, Wilson C M, Campbell N P S, Khan M M, Patterson G C, Webb S W, Adgey A A J) A double blind placebo controlled study of early and late administration of recombinant tissue plasminogen activator in acute myocardial infarction 316
MacPherson P C *see* Barin E S *et al*
Madden B *see* Coghlan J G *et al*
Madden S E *see* Skehan J D *et al*
Magee W H *see* Dickey W A *et al*
Maire R *see* Ikram S *et al*
Maisey M N *see* Baker E J *et al*
Najm Y C *et al*
Maisey M N *see* Parsons J M *et al*
Mansfield A *see* Andreotti F *et al*
Marchant B *see* Davies S *et al*
Davies S W *et al*
Markland C G (& Pugsley W G, Treasure T, Swanton R H) Is there a limit to operability in aortic stenosis? 126 *P*
Marrinan M *see* Withington P S *et al*
Martin R *see* Ladusans EJ *et al*
Martin R P *see* Qureshi S A *et al*
Walsh KP *et al*
Martin W *see* McGhie I *et al*
Tweddel A *et al*
Tweddel A C *et al*
Maseri A *see* Andreotti F *et al*
Crea F *et al*
Crossman D C *et al*
El-Tamimi H *et al*
Kaski J C *et al*
Khan M I *et al*
Pupita G *et al*

Maslowski A *see* White H D *et al*
Matsuda M *see* Onodera T *et al*
Maurer B *see* O'Sullivan J J *et al*
Meade T W *see* Thompson S G *et al*
Meany B *see* Bergman G *et al*
Jewitt D *et al*
Meany B T *see* Archard L C *et al*
Medina E O Robles de *see* Robles de Medina E O
Mehta D (& Gilmour S, Ward D E, Camm A J) Optimal atrioventricular delay at rest and during exercise in patients with dual chamber pacemakers. a non-invasive assessment by continuous wave Doppler 161
— (& Stewart J, Ward D E, Davies M J, Camm A J) Role of signal averaged electrocardiograms compared with myocardial biopsy specimens in ventricular tachycardia associated with no obvious cardiac abnormality 102 *P*
— (& Odawara H, McKenna W J, Davies M J, Camm A J) Significance of frontal plane axis in non-ischaemic right ventricular tachycardias: echocardiographic and histological evaluation 474 *P*
— (& Ward D E, Camm A J) Reproducibility of non-ischaemic right ventricular tachycardias induced by exercise 474 *P*
Meijler F L (& Fisch C) Does the atrioventricular node conduct? review 309
Melcher D H *see* Kirkham N *et al*
Melton L J *see* Codd M B *et al*
Sugrue D D *et al*
Metcalfe J *see* Bergman G *et al*
Metcalfe M J (& Chan-Wah-Hak N S, Jennings K) The effects of treatment with felodipine as a single agent in coronary artery disease 258
Mey C de *see* de Mey C
Meyer J *see* Sutherland G R *et al*
Michelson J K *see* Stewart R A *et al*
Micklewright J *see* Griffith M J *et al*
Mikalian H *see* Ino T *et al*
Miller H C *see* Bloomfield P *et al*
Mills P *see* Monaghan M J & Mills P
Mills P G *see* Ambepitiya G *et al*
de Belder M A *et al*
Khan B *et al*
Skehan J D *et al*
Misawa T *see* Kinoshita O *et al*
Mishra A *see* Balcon R *et al*
Mitchell A G *see* Barbir M *et al*
Coghlan J G *et al*
Mitchell M M *see* van Daele M E R M *et al*
Mittal R B (& Ahmed A, John R, Lui D, Jarrit P H, Ell P J, Swanton R H) Myocardial perfusion SPET scintigraphy with technetium-99 methoxy-isobutyl-isonitrile in coronary artery disease: comparison with thallium 201 119 *P*
Moesby R *see* Pepper J R *et al*
Mohiaddin R H (& Underwood S R, Firmin D N, Abdulla A K, Rees R S O, Longmore D B) Magnetic resonance chemical shift imaging of human atheroma 119 *P*
— *see also* Underwood S R *et al*
Mohr-Kahaly S *see* Sutherland G R *et al*
Mok Q (& Ross-Russell R, Shinebourne E A) Prospective study of the frequency of phrenic nerve paralysis after cardiac surgery in children 99 *P*
Mokrane A *see* Shenasa M *et al*
Molajo A O (& Bennett D H, Bray C L) Is left ventricular dysfunction in mitral stenosis caused by isolated posterobasal wall abnormality? 98 *P*
Monaghan M *see* Jewitt D *et al*
Monaghan M J (& Chambers J B, Jackson G, Jewitt D E) The role of echocardiography and Doppler and colour flow mapping before, during, and after dilatation of the mitral valve 79 *P*
— (& Mills P) Doppler colour flow mapping: technology in search of an application?: review 133
Monro J L *see* Balaji S *et al*
Sutherland G R *et al*
Montarello J K *see* Rosenthal E *et al*
Montorsi P *see* Polonia J J *et al*
Moore D P (& Gilligan D, Oakley C M) Hypocapnia during exercise testing in dilated cardiomyopathy and hypertrophic cardiomyopathy: objective assessment by respiratory gas analysis 435 *P*
Morady F *see* Stewart R A *et al*
Morgan J M (& Gray H H, Oldershaw P J) The place of aortography and computed tomographic scanning in the investigation of suspected acute thoracic aortic dissection 466 *P*
— (& Raposo L, Clague J C, Chow W H, Oldershaw P J) Restrictive cardiomyopathy and constrictive pericarditis non-invasive distinction by digitised M mode echocardiography 29
Morrison E A *see* Kirkham N *et al*
Morrison W L (& Petch M C, Scrimgeour C, Rennie M J) Skeletal muscle and whole body protein turnover in cardiac failure 459 *P*
Morton J *see* Dominiczak A *et al*
Morton J J *see* McAlpine H *et al*
Morton P *see* Murphy P P *et al*
Richardson S G *et al*
Mulcahy D (& Keegan J, Sparrow J, Park A, Wright C, Fox K) Is there any indication to perform ambulatory ST segment monitoring in patients with coronary disease and a negative exercise test? 106 *P*
— — (& Lindsay D, Sparrow J, Park A, Wright C, Fox K) Silent myocardial ischaemia in patients referred for coronary bypass surgery because of angina: a comparison with patients whose symptoms were well controlled on medical treatment 496
— — (& Wright C, Sparrow J, Park A, Fox K) Is silent ischaemia common in patients with coronary artery disease and angina receiving standard medical treatment? 445 *P*
Mulligan I P (& Fraser A G, Lewis M J, Henderson A H) Effects of enalapril on myocardial noradrenaline overflow during exercise in patients with chronic heart failure 23
Munck O *see* Kelbæk H *et al*
Murakawa Y *see* Toda I *et al*
Murdoch I *see* Ladusans E J *et al*
Murphy P P (& Morton P, Murtagh J G, Scott M E, O'Keefe D B) Electrophysiological follow up of patients with sinus node disease paced with atrial demand pacemakers 467 *P*
Murray R G *see* Fox J P *et al*
Shaw T R D *et al*
Tan L B *et al*
Murrells T *see* Kirkham N *et al*
Murtagh J G *see* Murphy P P *et al*
Richardson S G *et al*
Musewe N N *see* Koike K *et al*
Musumeci F (& Lincoln C) Venous compared with anatomical repair for double outlet right ventricle with subpulmonary ventricular septal defect 89 *P*
— *see also* Aranki S *et al*
Aravot D *et al*

Nadazdin A (& Shahi M, Crake T, Foale R A) Syndrome X: abnormal left ventricular filling during dipyridamole echocardiography 478 *P*
Nadazdin A *see* Kambouroglou D *et al*
Nihoyannopoulos P *et al*
Najm Y C (& Timmis A D, Maisey M N, Pinies L M Y, Salinas A, Curry P V L, Sowton E) Coronary angioplasty and left ventricular function in single vessel coronary artery disease 262
Nakamura M *see* Okamatsu S *et al*
Nathan A W *see* Barin E S *et al*
Davies D W *et al*
Ratnatunga C P *et al*
Scriven A J I & Nathan A W
Wiseman M N & Nathan A W
Neubauer K *see* Sanderson J E *et al*
Nevin M (& Colchester A C F, Adams S, Pepper J R) The cerebral

function analysing monitor as the sole predictor of neurological damage after coronary artery bypass surgery 449 *P*
Newby A C *see* Angelini G D *et al*
Bryan A J *et al*
Newman S *see* Pugsley W *et al*
Venn G E *et al*
Nicholls D P *see* Elborn J S *et al*
Nicklas J M *see* Stewart R A *et al*
Nielsen D *see* Andersen H R *et al*
Nightingale P *see* Creamer J E *et al*
Nihoyannopoulos P (& Kambouroglou D, Nadazdin A, Joshi J, Ghosh P, Oakley C M) Assessment of mitral prostheses with transoesophageal echocardiography 471 *P*
— *see also* Gomez P *et al*
Kambouroglou D *et al*
Karatasakis G *et al*
McKenna W J *et al*
Taha T H *et al*
Norbury R N *see* de Belder M A *et al*
Norrell M S (& Lyons J P, Davies S, Timmis A D, Balcon R) Demonstration of myocardium at further risk after thrombolysis in acute myocardial infarction 116 *P*
— *see also* Coghlan J G *et al*
Norris R M *see* White H D *et al*
Northcote R J (& Canning G P, Ballantyne D) Electrocardiographic findings in male veteran endurance athletes 155
Northridge D *see* Findlay I N *et al*
Polonia J J *et al*
Northridge D B (& Findlay I N, Dilly S G, Dargie H J) Increase in plasma concentration of atrial natriuretic factor by atriopeptidase inhibition in heart failure: effects on diastolic function 458 *P*
Nouriel H (& Khan B, Burrell C J, Rothman M T) Long term follow up after percutaneous transluminal coronary angioplasty in patients with chronic total occlusions 94 *P*
Nozaki A *see* Toda I *et al*
Nugent S T *see* Finley J P *et al*

Oakley C *see* Gomez P *et al*
Karatasakis G *et al*
Taha T H *et al*
Yousif H *et al*
Oakley C M *see* McKenna W J *et al*
Moore D P *et al*
Nihoyannopoulos P *et al*
Oakley G D G *see* Bowes R J *et al*
O'Brien B *see* Ladusans E J *et al*
O'Brien W *see* Sutton P M I *et al*
Odawara H *see* Frenneaux M P *et al*
Mehta D *et al*
Odemuyiwa O *see* Ikram S *et al*
Peart I *et al*
Odom N *see* Hislop A A *et al*
O'Donoghue A *see* Counihan P J *et al*
Ogilvie D *see* Wordsworth P *et al*
Okamatsu S (& Takeshita A, Nakamura M) Impaired blood pressure response to exercise in patients with coronary artery disease: possible contribution of attenuated reflex vasoconstriction in non-exercising muscles 149
O'Kane H (& Cleland J, Gladstone D, Galvin I, Buckels J) Emergency operation after failed percutaneous angioplasty: how late? 93 *P*
O'Keeffe D B *see* Murphy P P *et al*
Richardson S G *et al*
Okubo S *see* Kinoshita O *et al*
Oldershaw P J *see* Morgan J M *et al*
Redington A N *et al*
Oldroyd K G *see* Rankin A C *et al*
Olsen E G *see* Archard L C *et al*
Olsson C G *see* Wilcox R G *et al*
Olsson S B *see* Blomstrom-Lundqvist C *et al*
Onodera T (& Fujiwara H, Tanaka M, Wu D-J, Matsuda M, Takemura G, Ishida M, Kawamura A, Kawai C) Cineangiographic and pathological features of the infarct related vessel in successful and unsuccessful thrombolysis 385
Ormiston J *see* White H D *et al*
O'Sullivan J J (& Conroy R, McKenna T, Maurer B) Silent ischaemia and QT prolongation in diabetic men with autonomic neuropathy 444 *P*

Pagé P *see* Shenasa M *et al*
Pai G R (& Rawles J M) The QT interval in atrial fibrillation 510
Palmer R B G *see* Sanderson J E *et al*
Paneth M *see* Luke R A *et al*
Pappageorgio G L (& Hudson N, Redding V J, Jones N B) Arteriographic underestimations of vessel diameter leading to overestimation of severity of stenosis 478 *P*
— (& Redding V J, Jones N B) Fibreoptic disposable catheter tip pressure transducer of very small dimensions for cardiovascular investigations 457 *P*
Parameshwar J (& Dambrink J-H E, Sparrow J, Wright C, Park A, Tweed J, Poole-Wilson P A) A new exercise test for the assessment of heart failure use of a self powered treadmill 421
— (& Shackell M, Richardson A, Poole-Wilson P A, Sutton G C) Prevalence of heart failure in two general practices 114 *P*
Park A *see* Mulcahy D *et al*
Parameshwar J *et al*
Parker D J *see* Wafa S S *et al*
Parsons J M (& Baker E J, Ladusans E J, Ayton V, Smith M A, Anderson R H, Deverall P B, Maisey M N, Tynan M J) Magnetic resonance imaging of atrioventricular septal defects in children correlates with echocardiographic, angiographic, and surgical findings 117 *P*
— (& Ladusans E J, Baker E J, Ayton V, Smith M A, Qureshi S A, Anderson R H, Tynan M J) Morphology of double outlet right ventricle (DORV) shown by magnetic resonance imaging 480 *P*
— — (& Qureshi S A, So L Y, Baker E J, Allan L, Tynan M J) Doppler analysis of blood flow in the superior vena cava clinical and echocardiographic correlation 481 *P*
— *see also* Baker E J *et al*
Ladusans E J *et al*
Qureshi S A *et al*
Pascalis C *see* Pugsley W *et al*
Pashazadeh M *see* Keogh B E *et al*
Patel N *see* Banner N R *et al*
Patterson G C *see* McNeill A J *et al*
Pattison C W (& Cumming D, Lovegrove C, Clayton-Jones D G, Dunn M J, Goldspink G, Yacoub M) The use of trained autologous skeletal muscle for long term counterpulsation in a sheep model 448 *P*
Patton H *see* Banner N R *et al*
Paul V *see* Farrell T G *et al*
Paul V E (& Garratt C J, Ward D E, Camm A J) Clinical assessment of rate adaptive pacing by the ventricular depolarisation gradient as the control parameter in a closed loop system 469 *P*
Peart I (& Bullock R E, Albers C, Hall R J C) Cold intolerance in patients with angina pectoris: effect of nifedipine and propranolol 521
— (& Odemuyiwa O, Albers C, Hall A, Kelly C, Hall R J C) Exercise testing soon after myocardial infarction its relation to course and outcome at one year in patients aged less than 55 years 231
Pedoe H Tunstall *see* Tunstall-Pedoe H
Pedoe H D Tunstall *see* Tunstall-Pedoe H D
Penketh R *see* Wharton J *et al*
Penkoske P A *see* Robertson M A *et al*
Penny W J (& Chesebro J H, Heras M, Bell M, Holmes D R, Vlietstra R E) Measurement of inflated balloon size during angioplasty importance of balloon material, artery size, and inflation pressure 447 *P*
— — — (& Badimon L, Fuster V) Thrombin inhibition by heparin or hirudin decrease platelet thrombus deposition and vasospasm after arterial angioplasty 117 *P*
Peploe M M Webb- *see* Webb-Peploe M M

Pepper J R (& Anderson D, Moesby R) Improved patency rates to small vessels with the internal mammary graft 109 *P*
— *see also* Nevin M *et al*
Perakis A *see* Rosenthal E *et al*
Pernot C *see* Brembrilla-Perrot B *et al*
Perrins E J *see* Baig M W *et al*
Perrot B Brembilla- *see* Brembilla-Perrot B
Perry R A *see* Hunt A G *et al*
Seth A *et al*
Petch M C *see* Hall J A *et al*
Morrison W L *et al*
Peto R *see* Chen Z *et al*
Collins R *et al*
MacMahon S *et al*
Phillips A N *see* Pocock S J *et al*
Phillips P A (& Sasadeus J, Hodsman G P, Horowitz J, Saltups A, Johnston C I) Plasma atrial natriuretic peptide in patients with acute myocardial infarction. effects of streptokinase 139
Pichené M *see* Brembilla-Perrot B *et al*
Pilai R *see* Aranki S *et al*
Pinties L M Y *see* Najm Y C *et al*
Pipilis A *see* Henderson R A *et al*
Sulke N *et al*
Pitt B *see* Stewart R A *et al*
Pocock S J (& Shaper A G, Phillips A N) High density lipoprotein cholesterol triglycerides, and ischaemic heart disease a reappraisal 106 *P*
Polak J M *see* Wharton J *et al*
Polonia J *see* McAlpine H *et al*
Polonia J J (& Montorsi P, Tonolo G, Leckie B, Northridge D, Dargie H, Richards A M) Haemodynamic and renal effects of low dose infusions of atrial natriuretic peptide in chronic heart failure 86 *P*
PolonieckI J D *see* McKenna W J *et al*
Stewart R A *et al*
Poole-Wilson P A *see* Parameshwar J *et al*
Poppele G *see* Sutherland G R *et al*
Porter A *see* Frenneaux M P *et al*
Prakash O *see* van Daele M E R M *et al*
Prescott R J *see* Bloomfield P *et al*
Price C (& Keenan D J M) Injury to a saphenous vein graft during removal of a temporary epicardial pacing wire electrode· case report 546
Priestley K (& Tynan M J, Curry P V L) Presentation of ventricular tachycardia in children 77 *P*
Priestley K A (& Tynan M J, Curry P V L) Complete heart block in children: How many will need a pacemaker? 481 *P*
Prigent F *see* Underwood S R *et al*
Pugh S E (& White N J, Aronson J K, Grahame-Smith D G, Bloomfield J G) Clinical, haemodynamic, and pharmacological effects of withdrawal and reintroduction of digoxin in patients with heart failure in sinus rhythm after long term treatment 529
Pugsley W (& Klinger L, Pascalis C, Harrison M, Newman S, Treasure T) Microemboli and cerebral impairment during cardiac surgery 463 *P*
— *see also* Griffin S *et al*
John R M *et al*
Markland C G *et al*
Pumphrey C W *see* de Belder M A *et al*
Skehan J D *et al*
Pupita G (& Kaski J C, Galassi A R, Crea F, Maseri A) Long term prognosis and variability of myocardial ischaemia in syndrome X 443 *P*
— *see also* Crea F *et al*
Pye M (& Bain W, Weerasana N, Hutton I, Cobbe S M) Doppler echocardiographic characteristics of prosthetic valves in the tricuspid position 92 *P*

Quaegebeur J *see* Angelini G *et al*
Sutherland G R *et al*
Qureshi S A (& Ladusans E J, Parsons J M, Baker E J, Tynan M J) Efficacy of percutaneous balloon dilatation of the pulmonary outflow tract as palliation of tetralogy of Fallot 482 *P*
— (& Martin R P, Dickinson D F, Hunter S) Balloon dilatation of stenosed Blalock-Taussig shunts 432
— *see also* Ladusans E J *et al*
Parsons J M *et al*

Radda G K *see* Arnolda L *et al*
Conway M *et al*
Radley-Smith R (& Yacoub M H) Heart and heart-lung transplantation in children 91 *P*
— *see also* Aravot D *et al*
Kirk C R *et al*
Ladusans E J *et al*
Rae A P *see* Burns J M A *et al*
Rankin A C *et al*
Raftery E B *see* Broadhurst P *et al*
DasGupta P *et al*
Hughes L *et al*
Hughes L O *et al*
Jain D *et al*
Lahiri A *et al*
Rahimtoola S H *see* Bhandari A K *et al*
Rajagopalan B *see* Arnolda L *et al*
Conway M *et al*
Ramhamdany E *see* DasGupta P *et al*
Rankin A C (& Rae A P, Oldroyd K G, Cobbe S M) Verapamil or adenosine for supraventricular tachycardia 123 *P*
Raposo L *see* Morgan J M *et al*
Ratnatunga C P (& Barin E S, Davies D W, Nathan A W, Edmondson S J) The epicardial approach to surgical treatment of Wolff-Parkinson-White syndrome 462 *P*
Raval U *see* Hughes L O *et al*
Jain D *et al*
Rawles J M *see* Pai G R & Rawles J M
Redding V J *see* Agarwal A K & Redding V J
Pappageorgio G L *et al*
Reddy B R *see* Boden W E *et al*
Redington A N (& Shinebourne E A, Rigby M L, Oldershaw P J) The effect of loading conditions on the right ventricular pressure-volume association 81 *P*
Rees M R (& Gehani A A, Feith F) Percutaneous angioscopy 86 *P*
— *see also* Gehani A A *et al*
Rees P G *see* Sullivan I D *et al*
Rees R S O *see* Mohiaddin R H *et al*
Underwood S R *et al*
Reid C J *see* Barbir M *et al*
Reid J M *see* Houston A B *et al*
Reidy J *see* Rosenthal E *et al*
Rennie M J *see* Morrison W L *et al*
Rennoliet H *see* Sutherland G R *et al*
Richards A M *see* Polonia J J *et al*
Richardson A *see* Parameshwar J *et al*
Richardson P J *see* Archard L C *et al*
Richardson S G (& Allen D C, Morton P, Murtagh J G, Scott M E, O'Keeffe D B) Pathological changes after intravenous streptokinase treatment in eight patients with acute myocardial infarction 390
Rickards A *see* Cunningham D *et al*
Rigby M L *see* Carvalho J *et al*
Carvalho J S *et al*
Redington A N *et al*
Ritter M *see* Jenni R *et al*
Rivers J T *see* White H D *et al*
Riyami A Al *see* Al-Riyami A
Roberts R *see* Boden W E *et al*
Robertson M A (& Byrne P J, Penkoske P A) Perinatal management of critical aortic valve stenosis diagnosed by fetal echocardiography. case report 365

ROBERTSON P *see* Sreeram N *et al*
ROBISON A K *see* Fox K A A *et al*
ROBLES DE MEDINA E O *see* Hauer R N W *et al*
ROBSON R H (& Holmes K M, Bexton R) Stress testing a district audit 98 *P*
ROBSON S C (& Furniss S S, Heads A, Boys R J, McGregor C, Bexton R S) Isometric exercise in the denervated heart: a Doppler echocardiographic study 224
ROELANDT J *see* Smyllie J *et al*
  Sutherland G R *et al*
  Taams M A *et al*
ROELANDT J R T C *see* Fraser A G *et al*
  Smyllie J *et al*
  Smyllie J H *et al*
  Sutherland G R *et al*
  Van Daele M E R M *et al*
ROGERS W J *see* Buchalter M B *et al*
ROSE M *see* Archard L C *et al*
ROSENTHAL E (& Montarello J K, Perakis A, Boyd E, Deverall P, Yates A, Sowton E, Curry P) Balloon dilatation of the aortic valve. an in vitro assessment of the mechanism, magnitude, and duration of its effects 92 *P*
— — — — — — — — Normal and stenotic aortic valve area measurement· comparison of an in vitro physiological method with Doppler echocardiography 102 *P*
— — Reidy J, Yates A K, Curry P V L) From peripheral to coronary arteries: experience with percutaneous laser thermal angioplasty 99 *P*
ROSS-RUSSELL R *see* Mok Q *et al*
ROTHMAN M *see* Balcon R *et al*
  Davies S *et al*
  Gerschlick A H *et al*
ROTHMAN M T *see* Burrell C J *et al*
  Davies S W *et al*
  de Belder M A *et al*
  Gerschlick A H *et al*
  Nouriel H *et al*
  Skehan J D *et al*
ROWE R D *see* Ino T *et al*
ROWLAND E *see* Cunningham D *et al*
ROYSTON D *see* Bidstrup B P *et al*
RUANE B *see* Burke E *et al*
RUDD R *see* Davies S *et al*
  Davies S W *et al*
RUDIN A *see* Blomstrom-Lundqvist C *et al*
RULF E N *see* van Daele M E R M *et al*
RUMLEY A *see* McAlpine H *et al*
RUNNALS M E *see* Sutton P M I *et al*
  Taggart P *et al*
RUOCCO N A *see* Glazier J J *et al*
RUSSELL A E *see* Smith S A *et al*
RUSSELL R ROSS- *see* Ross-Russell R
RYAN T J *see* Glazier J J *et al*

SALIH M *see* Fox J P *et al*
SALIH M S *see* Fox J P *et al*
SALINAS A *see* Najm Y C *et al*
SALMON A P (& Holder R, De Giovanni J V, Wright J G G, Silove E D) Effects of digoxin in infants with ventricular septal defects and cardiac failure 115 *P*
SALTISSI S *see* Currie P & Saltissi S
  Higham P D *et al*
SALTUPS A *see* Phillips P A *et al*
SAMPSON M J *see* Chambers J B *et al*
SAMSTAD S O (& Hegrenaes L, Skjaerpe T, Hatle L) Half time of the diastolic aortoventricular pressure difference by continuous wave Doppler ultrasound. a measure of the severity of aortic regurgitation? 336
SANDERSON J E (& Waterhouse T D, Palmer R B G) Epidural spinal stimulation in patients with intractable angina 462 *P*
— (& Whiteley E, Neubauer K) Management of patients after myocardial infarction Do exercise testing and a more intensive approach make any difference? 454 *P*
SANKOORIKAL A *see* Bhandari A K *et al*
SAPSFORD R N *see* Bidstrup B P *et al*
SASADEUS J *see* Phillips P A *et al*
SAVARD P *see* Shenasa M *et al*
SCHECHTMAN K B *see* Boden W E *et al*
SCHMID E R *see* Jenni R *et al*
SCHORK M A *see* Stewart R A *et al*
SCHWARTZ D J *see* Boden W E *et al*
SCHWARTZ R C *see* Henney A M *et al*
SCOTT M E *see* Murphy P P *et al*
  Richardson S G *et al*
SCOTT N *see* McMurray J *et al*
SCRIMGEOUR C *see* Morrison W L *et al*
SCRIVEN A J I (& Nathan A W) Laser-generated tissue debris causes considerable platelet aggregation in vitro 447 *P*
SEMPLE P *see* Dominiczak A *et al*
SERRUYS P W *see* Beatt K J *et al*
SETH A (& Perry R A, Hunt A E, Shiu M F) Clinical outcome and procedural risks of complete compared with incomplete revascularisation by percutaneous transluminal coronary angioplasty in patients with multivessel disease 79 *P*
— — (Smith S, Shiu F F) Myocardial protection with diltiazem during coronary angioplasty cardioplegic or vasodilatory action? 439 *P*
— *see also* Hunt A G *et al*
SHACKELL M *see* Parameshwar J *et al*
SHAHI M *see* Cleland J F *et al*
  Nadazdin A *et al*
SHAPER A G (& Wannamethee G, Walker M) Alcohol and cardiovascular mortality 88 *P*
— *see also* Cook D G & Shaper A G
  Davies S W *et al*
  Pocock S J *et al*
  Whincup P H *et al*
SHAPIRO E P *see* Buchalter M B *et al*
SHARABANI R *see* Cleland J F *et al*
SHARIF D S *see* Abinader E G & Sharif D S
SHARIF H *see* Arnolda L *et al*
SHARPE N *see* White H D *et al*
SHAW T R D (& McAreavey D, Essop A R, Song C S) Balloon dilatation of the mitral valve for "inoperable" mitral stenosis 452 *P*
— (& Starkey I R, Essop A R, Sutton R, Davies M K, Murray R G, Littler W A) Emergency coronary bypass surgery after vessel occlusion at angioplasty in centres without on-site facilities for cardiac surgery 438 *P*
— *see also* Flapan A D *et al*
SHENASA J *see* Shenasa M *et al*
SHENASA M (& Cardinal R, Shenasa J, Vermeulen M, Kaltenbrunner W, Pagé P, Savard P) New insights with computerised intraoperative epicardial mapping of QRS alternans during orthodromic tachycardia 96 *P*
— (& Mokrane A, Lacroix D, Dubuc M, LeBlanc A-R) Demonstration of the fatigue and slow recovery in the human atrioventricular node 103 *P*
SHEPPARD J M *see* Smith S A *et al*
SHEPPARD M C *see* Gammage M D *et al*
SHEPSTONE B *see* Conway M A *et al*
SHERIDAN D J *see* Chakrabarty S *et al*
  Winterton S J *et al*
SHINEBOURNE E A *see* Carvalho J *et al*
  Carvlho J S *et al*
  Mok Q *et al*
  Redington A N *et al*
  Till J A *et al*
SHIU F F *see* Seth A *et al*
SHIU M F *see* Hunt A C *et al*
  Hunt A G *et al*
  Seth A *et al*

Shore D F *see* Balaji S *et al*
Silove E D *see* Salmon A P *et al*
Simpson I A Value of colour Doppler flow mapping and digital computer analysis in the measurement of mitral regurgitation in vitro 106 *P*
Skehan J D (& Carey C M, de Belder M A, Madden S E, Pumphrey C W, Rothman M T, McDonald A H) Clinical experience of coronary angiography by the femoral route using a multipurpose catheter (Sones technique from the leg) 108 *P*
— (& Cowley M L, Burrell C J, Barrett C W, Mills P G) Thrombolysis for acute myocardial infarction: is there adequate provision in England? 453 *P*
— *see also* de Belder M A *et al*
Khan B *et al*
Skehan J D *see* Khan B *et al*
Skene A *see* Wilcox R G *et al*
Skjaerpe T *see* Samstad S O *et al*
Sleight P *see* Arnolda L *et al*
Conway M A *et al*
Sleight P for ISIS Collaboration Group *see* Collins R *et al*
Smallhorn J F *see* Koike K *et al*
Leung M P *et al*
Smith A *see* Wharton J *et al*
Smith D G Grahame *see* Grahame-Smith D G
Smith L D R Evidence for active filling of the left ventricle a study of the association of ventricular torsion and ventricular volume 113 *P*
— (& Katritsis D, Webb-Peploe M M) Use of a hollow wire to facilitate angioplasty of occluded vessels 326
Smith M A *see* Baker E J *et al*
Parsons J M *et al*
Smith P *see* Kambouroglou D *et al*
Smith R (& Brender D, McCredie M) Percutaneous transluminal balloon dilatation of the mitral valve in pregnancy: case report 551
Smith R Radley *see* Radley-Smith R
Smith R C Radley *see* Radley-Smith R C
Smith S *see* Seth A *et al*
Smith S A Pitfalls and limitations in the use of impedance cardiography correspondence reply 129
— (& Stoner J E, Russell A E, Sheppard J M, Aylward P E) Transmitral velocities measured by pulsed Doppler in healthy volunteers: effects of acute changes in blood pressure and heart rate 344
Smith T *see* Jain D *et al*
Smith W C S *see* Crombie I K *et al*
Tunstall-Pedoe H *et al*
Smyllie J (& Sutherland G R, Roelandt J) Diagnosis of left ventricular pseudoaneurysm by colour Doppler flow mapping 81 *P*
— — van Daele M, Roelandt J R T C) Colour flow mapping in the detection of intracardiac fistulas after aortic valve surgery for endocarditis 49 *P*
— — (Visser C, Zwiers G, Roelandt J, Dawkins K, Conway N) Range of coronary artery lesions and the requirement for coronary arteriography in post-infarct ventricular septal defects 114 *P*
Smyllie J H (& Sutherland G R, Roelandt J R T C) Demonstration of the ascending aorta in infective endocarditis by intravenous digital subtraction angiography: correspondence 554
— *see also* Sutherland G R *et al*
Smyth D *see* Bergman G *et al*
So L Y *see* Parsons J M *et al*
Sobnack R *see* Levy R D *et al*
Solanki K *see* Levy R D *et al*
Somerset D *see* Luke R A *et al*
Song C S *see* Shaw T R D *et al*
Soper N *see* Conway M A *et al*
Sowton E *see* Bucknall C *et al*
Henderson R A *et al*
Najim Y C *et al*
Rosenthal E *et al*
Sulke N *et al*
Soyombo A *see* Angelini G D *et al*
Sparrow J *see* Mulcahy D *et al*
Sparrow J *see* Parameshwar J *et al*
Sprigings D C (& Chambers J B, Cochrane T, Allen J, Black M M, Jackson G) Ventricular stroke work loss: an alternative method of quantifying the severity of aortic stenosis 451 *P*
— *see also* Chambers J B *et al*
Sreeram N (& Hunter S, Wren C) Acute myocardial infarction in infancy· unmasking of anomalous origin of the left coronary artery from the pulmonary artery by ligation of an arterial duct: case report 307
— (& Wren C, Bhate M, Robertson P, Hunter S) Cardiac abnormalities in the fragile X syndrome 289
Stanford C F *see* Elborn J S *et al*
Starkey I R *see* Shaw T R D *et al*
Stewart J *see* Mehta D *et al*
Stewart R *see* Karatasakis G *et al*
Stewart R A (& McKenna W J, Poloniecki J D, Michelson J K, Das S K, Morady F, Schork M A, Pitt B, Nicklas J M) Prospective, randomised, double blind, placebo controlled trial of low dose amiodarone in patients with severe heart failure and frequent ventricular extrasystoles 459 *P*
Stimmler L *see* Virginia M *et al*
Stockins B *see* Yousif H *et al*
Stoner J E *see* Smith S A *et al*
Straughan K *see* Burrell C J *et al*
Sturman S *see* Ahmad R A S *et al*
Sturridge M F *see* John R M *et al*
Sugimoto T *see* Toda I *et al*
Sugrue D D (& Codd M B, Melton L J, Gersh B J) The national history of idiopathic dilated cardiomyopathy: a comparison of population based and referred cohorts 88 *P*
— *see also* Codd M B *et al*
Sulke N (& Pipilis A, Karani S, Bucknall C, Sowton E) Paced and natural rate response during everyday activity 476 *P*
— *see also* Bucknall C *et al*
Sullivan I D (& Cooper S G, Bull C, Taylor J F N) Percutaneous balloon dilatation may relieve pulmonary venous pathway obstruction after Mustard's operation for transposition of the great arteries 472 *P*
— — (Wren C) Is balloon dilatation the treatment of choice for aortic recoarctation? 480 *P*
— (& Wren C, Bain H, Hunter S, Rees P G, Taylor J F N, Bull C, Deanfield J E) Balloon dilatation of the aortic valve for congenital aortic stenosis in childhood 186
— *see also* Franklin R C G *et al*
Suryapranata H *see* Beatt K J *et al*
Sutherland G R (& Geuskens R, Taams M A, Gussenhoven E J, Hess J, Roelandt J) Value of transoesophageal echocardiography in adolescents and adults with congenital heart disease 480 *P*
— (& McGhie J, Monro J L, Quaegebeur J) Colour flow mapping as intraoperative angiography in ventricular septal defects: advantages and pitfalls? 127 *P*
— (& Poppele G, Langenstein B, Taams M, Roelandt J, Hanrath P) Transoesophageal echocardiography, an improved diagnostic technique for subaortic membranes 76 *P*
— (& Smylie J H, Roelandt J R T C) Advantages of colour flow imaging in the diagnosis of left ventricular pseudoaneurysm 59, 81 *P*
— (& Taams M A, Gussenhoven W J, Erbel R, Rennollet H, Engerding R, Visser C, Koolen J, Daniel W, Jaarsma W, Mohr-Kahaly S, Roelandt J, Meyer J) Role of transoesophageal echocardiography in the diagnosis of aortic dissection: a cooperative multicentre trial 125 *P*
— *see also* Balaji S *et al*
Fraser A G *et al*
Smyllie J *et al*
Smyllie J H *et al*
Taams M A *et al*
Van Daele MERM *et al*
Sutton G C *see* Parameshwar J *et al*

SUTTON P M I (& Taggart P, Treasure T, O'Brien W, Runnals M E) Do tight coronary stenoses impede access of cold cardioplegia protection or not? 109 *P*
— *see also* Taggart P *et al*
SUTTON R *see* Fitzpatrick A *et al*
Shaw T R D *et al*
SWANTON R H *see* John R M *et al*
Markland C G *et al*
Taggart P *et al*
Underwood S R *et al*
SYKES B *see* Wordsworth P *et al*
SYKES R M *see* Dashwood M R *et al*
SYNDERCOMBE-COURT D *see* Gershlick A H *et al*

TAAMS M *see* Sutherland G R *et al*
TAAMS M A (& Gussenhoven W J, Bom N, Roelandt J, Sutherland G R) Comparative value of precordial and transoesophageal echocardiography in the spectrum of infective endocarditis 93 *P*
— *see also* Sutherland G R *et al*
TAGGART P (& Sutton P M I, John R, Hayward R, Runnals M E, Swanton R H) Epicardial electrogram during successive balloon occlusion during percutaneous transluminal coronary angioplasty 84 *P*
— — Runnals M E, Lab M J, Swanton R H) Contraction excitation feedback: a new approach 111 *P*
— *see* Sutton P M I *et al*
TAHA T *see* Yousif H *et al*
TAHA T H (& Barbir M, Nihoyannopoulos P, Yousif H, Dahan S, Trayner I, Thompson G R, Oakley C) Coronary artery ectasia: prevalence, frequency of hyperlipidaemia, and influence on myocardial perfusion 82 *P*
TAI Y T *see* Dougeni-Christacou V *et al*
TAJKARIMI S *see* Aranki S *et al*
TAKAYAMA M *see* White H D *et al*
TAKEMURA G *see* Onodera T *et al*
TAKESHITA A *see* Okamatsu S *et al*
TAMIMI H EL *see* El-Tamimi H
TAN L B (& Murray R G, Littler W A) Comparison of the haemodynamic effects of dopexamine and dobutamine in patients with severe heart failure 87 *P*
TANAKA M *see* Onodera T *et al*
TAVENDALE R *see* Tunstall-Pedoe H *et al*
TAYLOR J F N *see* Sullivan I D *et al*
TAYLOR K M *see* Bidstrup B P *et al*
Keogh B E *et al*
THEODORAKIS G *see* Fitzpatrick A *et al*
THOMAS J *see* Luke R A *et al*
THOMAS P *see* Chakrabarty S *et al*
Winterton S J *et al*
THOMAS S *see* Bergman G *et al*
Jewitt D *et al*
THOMPSON G R *see* Barbir M *et al*
Taha T H *et al*
THOMPSON S G (& Greenberg G, Meade T W) Risk factors for stroke and myocardial infarction in women in the United Kingdom as assessed in general practice: a case-control study 403
TILL J A (& Jones S, Shinebourne E A, Ward D E) Long term follow up of endocardial pacing in children of 15 kg or less 467 *P*
TIMMIS A *see* Davies S *et al*
Gershlick A H *et al*
TIMMIS A D *see* Ambepitiya G *et al*
Davies S W *et al*
Gerslick A H *et al*
Henderson R A *et al*
Najm Y C *et al*
Norell M S *et al*
TODA I (& Kawahara T, Murakawa Y, Nozaki A, Kawakubo K, Inoue H, Sugimoto T) Electrophysiological study of young patients with exercise related paroxysms of palpitation: role of atropine and isoprenaline for initiation of supraventricular tachycardia 268
TODD I C (& Ballantyne D) Effect of exercise training on myocardial perfusion in angina pectoris 107 *P*
TONOLO G *see* Polonia J J *et al*
TOYAMA M (& Amano A, Kameda T) Familial aortic dissection: a report of rare family cluster 204
TRAVILL C *see* Fitzpatrick A *et al*
TRAYNER I *see* Taha T H *et al*
TREASURE T *see* Griffin S *et al*
John R M *et al*
Markland C G *et al*
Pugsley W *et al*
Sutton P M I *et al*
Venn G E *et al*
TRUSLER G A *see* Leung M P *et al*
TSIPOURAS P *see* Henney A M *et al*
TUNSTALL-PEDOE H (& Smith W C S, Tavendale R) Cholesterol management algorithms and British serum cholesterol concentrations: implications of the Scottish Heart Health and MONICA Studies 460 *P*
TUNSTALL-PEDOE H D *see* Crombie I K *et al*
TURINA M *see* Goy J-J *et al*
Jenni R *et al*
TURNER M A *see* Winterton S J *et al*
TWEDDEL A (& Martin W, Hutton I) Is syndrome X a variable degree of myopathy? 74 *P*
— — McGhie I, Hutton I) Is the site of myocardial ischaemia reproducible? 107 *P*
— *see also* McGhie I *et al*
TWEDDEL A C (& Martin W, McGhie I, Hutton I) Response of flow and distribution to stress in normal coronary arteries 476 *P*
TWEED J *see* Parameshwar J *et al*
TYNAN M *see* Ladusans E J *et al*
TYNAN M J *see* Baker E J *et al*
Ladusans E J *et al*
Parsons J M *et al*
Priestley K *et al*
Priestley K A *et al*
Qureshi S A *et al*

UNDERWOOD S *see* Davies S *et al*
UNDERWOOD S R (& Prigent F, Mohiaddin R H, Rees R S O, Longmore D B) Magnetic resonance imaging of cardiac sarcoidosis 103 *P*
— (& Walton S, Laming P J, Ell P J, Emanuel R W, Swanton R H) Quantitative phase analysis in the assessment of coronary artery disease 14
— *see also* Mohiaddin R H *et al*

VAN BOVEN V *see* Angelini G *et al*
VANCHERI F (& Gibson D) Relation of third and fourth heart sounds to blood velocity during left ventricular filling 144
VAN DAELE M *see* Smyllie J *et al*
VAN DAELE M E R M (& Sutherland G R, Mitchell M M, Prakash O, Rulf E N, Roelandt J R T C) Is pulmonary wedge pressure a good index of intraoperative myocardial ischaemia? A correlative electrocardiographic and transoesophageal echocardiographic study 477 *P*
— *see also* Fraser A G *et al*
VAN HERWERDEN L *see* Fraser A G *et al*
VARMA M P S *see* Burke E *et al*
VARRICCHIONE T R *see* Glazier J J *et al*
VEJAR M *see* Kaski J C *et al*
VENN G E (& Klinger L, Newman S, Harrison M, Treasure T) Intraoperative cerebral monitoring with a cerebral function analysing monitor predicts neuropsychological outcome after coronary artery surgery 110 *P*
VERMEULEN M *see* Shenasa M *et al*
VIELI A *see* Jenni R *et al*
VIRGINIA M (& Machado L, Stummler L, Edwards D, Allan L) Acceleration time in the aorta and pulmonary artery in prenatal life and in the newborn in the first week of life 77 *P*

Visser C *see* Smyllie J *et al*
Sutherland G R *et al*
Vlietstra R E *see* Bell M R *et al*
Penny W J *et al*
Von der Lippe G *see* Wilcox R G *et al*

Waagstein F *see* Herlitz J *et al*
Wafa S S (& Ward D E, McKenna W J, Parker D J, Camm A J) Efficacy of flecainide for atrial arrhythmias after open heart surgery 124 *P*
Wagner R *see* Caforio A *et al*
Wah-Hak N S Chan- *see* Chan-Wah-Hak N S
Walesby R *see* Davies S *et al*
Walker D R *see* Brooks S G *et al*
Walker J M (& Liu J Y) Is the negative inotropy of angiotensin converting enzyme inhibitors the result of prevention of angiotensin II activity in human atrial muscle? 441 *P*
Walker M *see* Shaper A G *et al*
Whincup P H *et al*
Walport M *see* Gomez P *et al*
Walsh K P (& Martin R P, Arnold R) Percutaneous balloon dilatation for critical pulmonary stenosis in neonates and infants 77 *P*
Walsh M *see* Black F *et al*
Walton S *see* Underwood S R *et al*
Wannamethee G *see* Shaper A G *et al*
Ward D E *see* Cripps T et al
Farrell T *et al*
Garratt C J *et al*
Griffith M J *et al*
Mehta D *et al*
Paul V E *et al*
Till J A *et al*
Wafa S S *et al*
Waterfield S A *see* Barin E S *et al*
Waterhouse T D *see* Sanderson J E *et al*
Watling M I L *see* Davies S W *et al*
Watson R D S *see* Ahmad R A S *et al*
Webb D *see* Counihan P J *et al*
Frenneaux M P *et al*
Webb S W *see* McNeill A J *et al*
Webb-Peploe M M *see* Cooper I C *et al*
Katritsis D *et al*
Smith L D R *et al*
Wedzicha J *see* Davies S *et al*
Wedzicha J A *see* Davies S W *et al*
Weerasana N *see* Pye M *et al*
Weisfeldt M L *see* Buchalter M B et al
Weiss J L *see* Buchalter M B *et al*
Westerhof P W *see* Hauer R N W *et al*
Wharton J (& Anderson R H, Espejo R, Smith A, Penketh R, Polak J M) Development of peptide containing neural and endocrine elements in the human heart 112 *P*
Wheatley D J *see* Bloomfield P *et al*
Whincup P H (& Cook D G, Shaper A G, Macfarlane D, Walker M) Childhood blood pressure measurements in nine British towns 76 *P*
White D G *see* Withington P S *et al*
White H D (& Rivers J T, Norris R M, Takayama M, Maslowski A, Hart H, Sharpe N, Ormiston J) Comparison of recombinant tissue plasminogen activator and streptokinase for preservation of left ventricular function after myocardial infarction 72 *P*
White N J *see* Pugh S E *et al*
Whiteley E *see* Sanderson J E *et al*
Wickens D *see* Davies S *et al*
Wilcox R G (& von der Lippe G, Olsson C G, Jensen G, Skene A, Hampton J R) Anglo-Scandinavian study of early thrombolysis with recombinant tissue plasminogen activator (rt-PA): a six month mortality study 71 *P*
Wilkinson P *see* Davies S *et al*
Williams B C *see* Flapan A D *et al*
Williams D *see* Goudevenos J *et al*
Williams H M J *see* Bryan A J *et al*
Williams J D *see* Lewis N P *et al*
Williams J R *see* Burke E *et al*
Williams T *see* Chakrabarty S *et al*
Williams W G *see* Leung M P *et al*
Wilson C M *see* McNeill A J *et al*
Wilson J T *see* Findlay I N *et al*
Wilson N *see* Brooks S G *et al*
Wilson P A Poole *see* Poole-Wilson P A
Winner S J (& Boon N A) Hazards associated with the use of temporary pacemakers before permanent pacing 96 *P*
Winterton S J (& Thomas P, Turner M A, Sheridan D J) Effects of cardiac hypertrophy on cellular electrophysiology during normal and ischaemic perfusion 442 *P*
Wiseman M N (& Dyke L J, Dymond D S) Whole bolus ratio: a new technique for assessing valvar regurgitation from first pass radionuclide angiography 465 *P*
— (& Nathan A W) Reversion of atrial fibrillation. intravenous flecainide versus intravenous disopyramide 470 *P*
— *see also* Levy R D *et al*
Withington P S (& Graham T R, Marrinan M, White D G, Colvin P, Lewis C T) Medium term cardiovascular effects of implantable left ventricular assist devices (LVADs) in the calf 464 *P*
Wong C Y *see* Davies D W *et al*
Wordsworth P (& Ogilvie D, Akhras F, Jackson G, Sykes B) Genetic segregation analysis of familial mitral valve prolapse shows no linkage to fibrillar collagen genes 300
Wren C (& Hunter S) Balloon dilatation of a stenosed bioprosthesis in the tricuspid valve position: case report 65
—— *see also* Sreeram N *et al*
Sullivan I D *et al*
Wright C *see* Mulcahy D *et al*
Parameshwar J *et al*
Wright J G C *see* Salmon A P *et al*
Wu D-J *see* Onodera T *et al*

Yacoub M *see* Crossman D C *et al*
Ledingham S J M & Yacoub M
Pattison C W *et al*
Yacoub M H *see* Aranki S *et al*
Aravot D *et al*
Archard L C *et al*
Banner N R *et al*
Barbir M *et al*
Dashwood M R *et al*
Kirk C R *et al*
Ladusans E J *et al*
Radley-Smith R & Yacoub M H
Yamada H *see* Kinoshita O *et al*
Yates A *see* Rosenthal E *et al*
Yates A K *see* Rosenthal E *et al*
Yousif H (& Lo E, Taha T, Stockins B, Oakley C) Diagnostic importance of reciprocal ST segment depression in acute myocardial infarction 121 *P*
— *see also* Taha T H et al
Yusuf S *see* MacMahon S *et al*

Zerhouni E A *see* Buchalter M B *et al*
Zwiers G *see* Smyllie J *et al*

SUBJECT INDEX
1989, Volume 61

P = Proceedings of the British Cardiac Society

- Acceleration time in the aorta and pulmonary artery in prenatal life and newborn (Virginia *et al*). 77 *P*
- Adenosine
  - and angina pectoris (Crea *et al*). 455 *P*
  - beneficial effect, during reperfusion after prolonged cardioplegic arrest (Ledingham & Yacoub). 442 *P*
  - during sinus rhythm showing latent pre-excitation (Garratt *et al*). 467 *P*
  - effect on pre-excitation induced by exercise (Garratt *et al*). 475 *P*
  - in termination of ventricular tachycardia, comparative efficacy and safety (Griffith *et al*). 123 *P*
  - or verapamil for supraventricular tachycardia (Ranking *et al*). 123 *P*
- Alcohol and cardiovascular mortality (Shaper *et al*) 88 *P*
  - related myocardial disease, immunological marker for (Cleland *et al*). 113 *P*
- Ambulatory ST segment, deviation after myocardial infarction, implications for exercise ischaemia and left ventricular function (Currie & Saltissi). 454 *P*
  - monitoring, indications to perform in coronary artery disease and negative exercise test (Mulcahy *et al*). 106 *P*
- Amiodarone in hypertrophic cardiomyopathy and ventricular tachycardia, long term survival (McKenna *et al*). 472 *P*
  - low dose, trial in severe heart failure and frequent ventricular extrasystoles (Stewart *et al*). 459 *P*
- Amyloid polyneuropathy, familial, impaired left ventricular diastolic filling (Kinoshita *et al*). 198
- Angina pectoris
  - and adenosine (Crea *et al*). 455 *P*
  - and cold intolerance, effect of nifedipine and propranolol (Peart *et al*) 532
  - in coronary artery disease, left ventricular filling and early diastolic function during (Dawson & Gibson). 248
  - and coronary artery disease receiving standard medical treatment, is silent ischaemia common (Mulcahy *et al*) 445 *P*
  - effect of exercise training on myocardial perfusion (Todd & Ballantyne). 107 *P*
  - intractable, and epidural stimulation (Sanderson *et al*). 462 *P*
  - perception in diabetes, evidence of silent exertional ischaemia (Ambepityia *et al*). 437 *P*
  - questionnaire, Rose, using (Cook & Shaper). 114 *P*
  - unstable, in association with saccular aneurysm of coronary artery, serial angiographic findings during development: case report (Goudevenos *et al*). 372
  - variant, spontaneous coronary spasm results from local coronary hyperreactivity to generalised constrictor stimulus (Kaski *et al*). 456 *P*
- Angiographic findings, serial, during development of saccular aneurysm of coronary artery in association with unstable angina· case report (Goudevenous *et al*). 372
- Angioplasty *see* Percutaneous transluminal coronary angioplasty
- Angiotensin converting enzyme inhibitors, negative inotropy, possible result of prevention of angiotensin II activity, human atrial muscle (Walker & Liu). 441 *P*
- Aortic
  - dissection, familial, report of rare family cluster (Toyama *et al*) 204
    - transoesophageal echocardiography in diagnosis, cooperative multicentre trial (Sutherland *et al*). 125 *P*
  - recoarctation, balloon dilatation as treatment of choice (Sullivan *et al*) 480 *P*
  - regurgitation, and pressure half time (Samstad *et al*). 336
  - root abscess complicating aortic valve endocarditis (John *et al*) 93 *P*
  - stenosis, congenital, in childhood, balloon dilatation of aortic valve (Sullivan *et al*). 186
    - critical, neonates with severe endocardial fibroelastosis, results of percutaneous balloon dilatation (Ladusans *et al*). 470 *P*
    - limit of operability (Markland *et al*). 126 *P*
    - ventricular stroke work loss as alternative method of quantifying severity (Sprigings *et al*). 451 *P*
  - valve, area, normal and stenotic, measurement, in vitro physiological method, and Doppler echocardiography compared (Rosenthal *et al*). 102 *P*
    - balloon dilatation, for congenital aortic stenosis in childhood (Sullivan *et al*). 186
      - mechanism, magnitude, and duration of effects (Rosenthal *et al*). 92 *P*
    - disease causing left ventricular hypertrophy, prevalence of ventricular arrhythmias (Al-Riyami *et al*). 450 *P*
    - endocarditis, aortic root abscess complicating (John *et al*). 93 *P*
    - homovital, homografts, evaluation (Aranki *et al*). 126 *P*
    - stenosis, critical, diagnosed by fetal echocardiography, perinatal management. case report (Robertson *et al*). 365
  - valvotomy for critical aortic stenosis, neonates and infants aged less than one year (Balaji *et al*). 358
- Aortography and computed tomographic scanning in investigation of suspected acute thoracic aortic dissection (Morgan *et al*). 466 *P*
- Aortoplasty, symmetrical, repair for supravalvar aortic stenosis (Angelini *et al*). 482 *P*
- Aprotinin effect on blood conservation during cardiac surgery (Bidstrup *et al*). 111 *P*
- Arcing with multiple high voltage low energy shocks in cardiac ablation (Barin *et al*). 469 *P*
- Arrhythmias
  - atrial, after open heart surgery, flecainide efficacy (Wafa *et al*). 124 *P*
  - in Bartter's syndrome, electrocardiographic findings and frequency (Blomstrom-Lundqvist *et al*). 274
  - life threatening, prediction in hypertrophic cardiomyopathy using high gain, signal averaged electrocardiography (Cripps *et al*). 124 *P*
  - during sleep in chronic heart failure (Davies *et al*). 458 *P*
  - ventricular, unassociated with acute myocardial infarction, electrophysiological study of survivors outside hospital (Dickey *et al*). 118 *P*
- Arteriographic underestimations of vessel diameter leading to overestimation of severity of stenosis (Pappageorgio *et al*). 478 *P*
- Arteriovenous bypass grafting, distension during surgical preparation reduces short term patency, pig (Bryan *et al*). 464 *P*
- Artificial valve, normal function, colour and continuous wave Doppler to assess (Kambouroglou *et al*). 126 *P*
- Aspirin, oral, and intravenous streptokinase in acute myocardial infarction, ISIS-2 large randomised trial (Collins *et al*). 71 *P*
- Atheroma, magnetic resonance chemical shift imaging (Mohiaddin *et al*) 119 *P*
- Atherosclerotic human coronary vessels preserve dilator response to substance P in vivo (Crossman *et al*). 455 *P*
- Atherosclerosis, evidence for increased tissue type plasminogen activator inhibitor complexes (Andreotti *et al*). 100 *P*
- Athletes, endurance, male veteran, electrocardiographic findings (Northcote *et al*). 155
- Atrial
  - arrhythmias after open heart surgery, flecainide efficacy (Wafa *et*

  al). 124 *P*
  fibrillation, mitral stenosis haemodynamic assessment (Davies *et al*). 116 *P*
    QT interval (Pai & Rawles). 510
    reversion, intravenous flecainide versus intravenous disopyramide (Wiseman & Nathan). 470 *P*
  flutter, spontaneous, 133 cases, electrophysiological characteristics and factors affecting successful conversion (Cunningham *et al*). 123 *P*
  pathology, left transoesophageal echocardiography to visualise (de Belder *et al*). 478 *P*
    pressure rise does not limit exercise capacity in hypertrophic cardiomyopathy (Frenneaux *et al*). 118 *P*
  natriuretic factor, plasma concentrations, increase by atriopeptidase inhibition in heart failure, diastolic function effects (Northridge *et al*). 458 *P*
    low dose infusions in chronic heart failure, haemodynamic and renal effects (Polonia *et al*) 86 *P*
    plasma, in myocardial infarction, effects of streptokinase (Phillips *et al*). 139
  septal defect, and sinus arrhythmia, children, analysis of heart rate variability before and after surgical repair (Finley *et al*). 280
Atrioventricular
  delay, optimal, at rest and during exercise, and dual chamber pacemakers, non-invasive assessment by continuous wave Doppler (Mehta *et al*) 161
  intervals, different, to improved exercise performance, importance, in patients in dual chamber pacemakers (Haskell & French). 46
  node, does it conduct: review (Meijler & Fisch). 309
    human, fatigue and slow recovery (Shenasa *et al*). 103 *P*
  septal defects, cross sectional echocardiography for recognition of ventricular topology (Carvalho *et al*). 285
    magnetic resonance imaging, correlates with echocardiographic, angiographic, and surgical findings, children (Parsons *et al*). 117 *P*
Atropine in initiation of supraventricular tachycardia (Toda *et al*). 268
Autoantibodies, novel cardiac specific circulating, in dilated cardiomyopathy (Caforio *et al*). 73 *P*
Autoimmune polyendocrinopathy and systemic hypertension, circulating autoantibodies against "myoendocrine" cells (Caforio *et al*). 457 *P*
Autologous skeletal muscle for long term counterpulsation, sheep (Pattison *et al*). 448 *P*

Balloon dilatation *see* Percutaneous transluminal coronary angioplasty
Baroreceptor sensitivity after myocardial infarction correlation with electrophysiological studies (Farrell *et al*). 472 *P*
Bartter's syndrome, electrocardiographic findings and arrhythmia frequency (Blomstrom-Lundqvist *et al*). 274
Beta$_2$ adrenoreceptor mediated activity, intracoronary injections of salbutamol to show (Hall *et al*). 108 *P*
Bifurcation lesions angioplasty in major coronary vessels (Bergman *et al*) 84 *P*
Bjork-Shiley prostheses, ten year results of randomised trial (Bloomfield *et al*). 452 *P*
Blalock-Taussig shunts, stenosed, balloon dilatation (Qureshi *et al*) 432
Blood
  flow, pulmonary, ratio to systemic, determination by continuous wave Doppler spectra (Jenni *et al*) 167
  pressure, impaired response to exercise in coronary artery disease (Okamatsu *et al*). 149
    measurements, childhood, nine towns, Britain (Whincup *et al*). 76 *P*
  velocity, relation of third and fourth heart sounds during left ventricular filling (Vancheri & Gibson). 144
Brachiocephalic vein, anomalous subaortic position, review and 3 new cases (Gerlis & Ho) 540
Bradycardia, propranolol induced, in tetralogy of Fallot: case report (Clark *et al*). 378
Breathlessness, lung function, and risk of heart attack (Cook & Shaper). 122 *P*
British Heart Journal, 50 year perspective: Jubilee editorial (Krikler). 1

Captopril
  does not potentiate action of loop diuretics in heart failure (Flapan *et al*). 87 *P*
  effect and free radical activity in chronic heart failure (McMurray *et al*). 457 *P*
  neuroendocrine responses, in acute heart failure after myocardial infarction (McAlpine *et al*). 81 *P*
Cardiac
  arrests, semiautomatic difibrillator accuracy during (Dickey *et al*). 98 *P*
  failure, experimental chronic, electrophysiological changes in animal model (Doherty). 104 *P*
  hypertrophy effects on cellular electrophysiology during normal and ischaemic perfusion (Winterton *et al*). 442 *P*
  rehabilitation after open heart surgery, return to work (Black *et al*). 448 *P*
Cardiogenic shock
  monitoring oxygen transport (Creamer *et al*) 445 *P*
  thrombolytic treatment (Burke *et al*). 88 *P*
Cardiolipin antibodies, raised, associated with systemic lupus erythematosus (Gomez *et al*). 80 *P*
Cardiomyopathy
  dilated, and enterovirus RNA in myocardium (Archard *et al*). 73 *P*
    distinction from anomalous origin of left coronary artery (Koike *et al*). 192
    epidemiological features (Codd *et al*). 80 *P*
    hypocapnia during exercise testing (Moore *et al*). 435 *P*
    idiopathic national history, population based and referred cohorts compared (Sugrue *et al*). 88 *P*
    novel cardiac specific circulating autoantibodies (Caforio *et al*). 73 *P*
  hypertrophic, abnormal peripheral vascular response, relation to clinical and prognostic features (Counihan *et al*). 456 *P*
    Doppler diastolic indices, association with functional capacity (Karatasakis *et al*). 100 *P*
    epidemiological features (Codd *et al*). 80 *P*
    evidence in abnormal vasodilator response (Frenneaux *et al*). 74 *P*
    exercise capacity, objective assessment (Frenneaux *et al*) 75 *P*
    hypocapnia during exercise testing (Moore *et al*) 435 *P*
    left atrial pressure rise does not limit exercise capacity (Frenneaux *et al*). 118 *P*
    prediction of life threatening arrhythmias using high gain, signal averaged electrocardiography (Cripps *et al*). 124 *P*
    and sustained uniform ventricular tachycardia, associated with left ventricular apical aneurysm (Alfonso *et al*). 178
    and ventricular tachycardia, long term survival with amiodarone (McKenna *et al*). 472 *P*
    without hypertrophy, description of two families with premature cardiac death and myocardial disarray in absence of increased muscle mass (McKenna *et al*). 75 *P*
  restrictive, and constrictive pericarditis, non-invasive distinction by digitised M mode echocardiography (Morgan *et al*). 29
Cardioplegia, cold, protection or not by tight coronary stenoses (Sutton *et al*) 109 *P*
Cardioplegic arrest, prolonged, beneficial effect of adenosine during reperfusion, after (Ledingham & Yacoub). 442 *P*
Cardioscint
  new system for continuous evaluation of left ventricular function (Lahiri *et al*) 102 *P*
  validation, system for continuous monitoring of left ventricular function (Broadhurst *et al*). 465 *P*

- Cardiovascular
  - disease, fatal, and diagonal earlobe creases, necropsy study (Kirkham *et al*). 361
  - mortality, and alcohol (Shaper *et al*). 88 *P*
- Cardioversion, transoesophageal DC (McKeown *et al*) 96 *P*
- Carpentier-Edwards prostheses, ten year results of randomised trial (Bloomfield *et al*) 452 *P*
- Catheter, multipurpose, clinical experience of coronary angiography by femoral route (Skehan *et al*). 108 *P*
- Central haemodynamic changes after meal (Kelbæk *et al*). 506
- Cerebral
  - function analysing monitor as sole predictor of neurological damage after coronary artery bypass surgery (Nevin *et al*). 449 *P*
  - impairment and microemboli during cardiac surgery, Doppler detection (Pugsley *et al*). 463 *P*
  - monitoring, intraoperative, with cerebral function analysing monitor predicts neuropsychological outcome after coronary artery surgery (Venn *et al*). 110 *P*
- Childhood blood pressure measurements, nine towns, Britain (Whincup *et al*). 76 *P*
- Cholesterol
  - management algorithms and British serum cholesterol concentrations (Tunstall-Pedoe *et al*). 460 *P*
  - serum, blood pressure and smoking in coronary artery disease (Chen *et al*). 460 *P*
- Coarctation hypertension induction, inositol phosphate production and proto-oncogene expression in left ventricle after, rat (Heagerty *et al*). 440 *P*
- Cold intolerance in angina pectoris, effect of nifedipine and propranolol (Peart *et al*). 521
- Collagen genes and mitral valve prolapse (Henney *et al*) 292 (Wordsworth *et al*) 300
- Collateral vessels, left ventricular damage and coronary disease, association after infarction and exercise (de Belder *et al*). 83 *P*
- Colour
  - and continuous wave Doppler to assess normal function of artificial valve (Kambouroglou *et al*). 126 *P*
  - Doppler flow mapping, and digital computer analysis value in measurement of mitral regurgitation in vitro (Simpson). 106 *P*
    - impact on assessment of congenital heart disease (Houston *et al*). 120 *P*
    - imaging advantages in diagnosis of left ventricular pseudoaneurysm (Sutherland *et al*). 59; 81 *P*
    - in detection of intracardiac fistulas after aortic valve surgery for endocarditis (Smyllie *et al*). 449 *P*
    - echocardiography, and Doppler, role before, during, and after mitral valve dilatation (Monaghan *et al*) 79 *P*
    - as intraoperative angiography in ventricular septal defects, advantages and pitfalls (Sutherland *et al*). 127 *P*
- Complete heart block, children, how many will need pacemaker (Priestley *et al*). 481 *P*
- Computed tomographic scanning, and aortography in investigation of suspected acute thoracic aortic dissection (Morgan *et al*) 466 *P*
- Congenital heart disease
  - colour Doppler flow mapping impact on assessment (Houston *et al*) 120 *P*
  - determination of left ventricular volumes by Simpson's rule, infants and children (Ino *et al*). 182
  - value of transoesophageal echocardiography, adolescents and adults (Sutherland *et al*). 480 *P*
- Constrictive pericarditis and restrictive cardiomyopathy, non-invasive distinction by digitised M mode echocardiography (Morgan *et al*). 29
- Contraction excitation feedback, new approach (Taggart *et al*). 111 *P*
- Coronary artery bypass surgery
  - because of angina, silent myocardial ischaemia in patients referred for, compared with those well-controlled on medical treatment (Mulcahy *et al*). 496
  - graft stenosis, stent implantation for treatment (Beatt *et al*). 446 *P*
  - intraoperative cerebral monitoring with cerebral function analysing monitor predicts neuropsychological outcome after (Venn *et al*). 110 *P*
  - cerebral function analysing monitor as sole predictor of neurological damage after (Nevin *et al*) 449 *P*
  - emergency, after vessel occlusion at angioplasty in centres without on-site facilities for cardiac surgery (Shaw *et al*). 438 *P*
- Coronary
  - arteries(y), chronically occluded, laser wire for percutaneous angioplasty (Bowes *et al*). 438 *P*
    - disease
      - and angina receiving standard medical treatment, is silent ischaemia common (Mulcahy *et al*). 445 *P*
      - associated with high insulin and C-peptide concentration, Asians (Hughes *et al*). 445 *P*
      - felodipine as single agent, effects of treatment (Metcalfe *et al*). 258
      - after heart transplantation, lipid abnormalities influence on development (Barbir *et al*) 462 *P*
      - impaired blood pressure response to exercise (Okamatsu *et al*). 149
      - left ventricular filling and early diastolic function during angina (Dawson & Gibson). 248
      - and negative exercise test, indications to perform ambulatory ST segment monitoring (Mulcahy *et al*). 106 *P*
      - quantitative phase analysis in assessment (Underwood *et al*). 14
      - relations of serum cholesterol, blood pressure and smoking habit (Chen *et al*). 460 *P*
      - single vessel, percutaneous transluminal coronary angioplasty and left ventricular function (Najm *et al*). 262
      - unemployment, and socio-environmental factors, Scotland (Crombie *et al*). 172
    - ectasia, prevalence, frequency of hyperlipidaemia, and influence on myocardial perfusion (Taha *et al*). 82 *P*
  - left anomalous, late left ventricular function after anatomical correction (Kirk *et al*). 110 *P*
    - anomalous origin from pulmonary trunk, distinction from dilated cardiomyopathy (Koike *et al*) 192
    - lesions range and requirement for coronary arteriography in post-infarct ventricular septal defects (Smyllie *et al*) 114 *P*
    - normal, response of flow and distribution to stress (Tweddel *et al*). 476 *P*
    - normal and diseased, densitometric angiographic assessment, validation of technique (de Belder *et al*). 115 *P*
    - occlusion, myocardial infarction during, platelets influence on extent (Chakrabarty *et al*) 78 *P*
  - atherogenesis, early, and myocardial infarction in Asians, and glucose metabolism (Hughes *et al*). 78 *P*
  - care unit, direct admission to, impact on thrombolytic treatment (Burns *et al*) 322
  - lesions, effect on results of percutaneous coronary angioplasty (Balcon *et al*). 446 *P*
  - ostial stenosis after radiotherapy, angioplasty or coronary artery surgery: case report (Handler *et al*). 208
  - spasm, spontaneous, variant angina results from local coronary hyperreactivity to generalised constrictor stimulus (Kaski *et al*). 456 *P*
  - thrombosis inhibition with low dose tissue plasminogen activator (t-PA) (Fox *et al*). 73 *P*
  - vessels, major, angioplasty of bifurcation lesions (Bergman *et al*). 84 *P*
- Correction 484
- Correspondence
  - Correcting a block?: successful experience of a small British pacing centre (Joseph) 212
  - Demonstration of the ascending aorta in infective endocarditis by intravenous digital subtraction angioplasty (Smyllie *et al*). 554
  - Influence of age on Doppler echocardiographic indices of left

  ventricular diastolic function (Abinader & Sharif). 483
  Pitfalls and limitations in the use of impedance cardiography (de Mey & Belz. Smith). 128
Counterpulsation, long term, use of trained autologous skeletal muscle, sheep (Pattison *et al*). 448 *P*
C-peptide and high insulin concentration associated with coronary disease, Asians (Hughes *et al*). 445 *P*
Cross sectional echocardiography for recognition of ventricular topology in atrioventricular septal defect (Carvalho *et al*). 285

Davies MJ Assistant Editor 3
Defibrillator
 current based, microprocessor controlled, initial experience (Dalzell *et al*). 502
  semiautomatic, accuracy during cardiac arrests (Dickey *et al*). 98 *P*
Denervated heart, and isometric exercise, Doppler echocardiographic study (Robson *et al*). 224
Diabetes perception of angina, evidence of silent exertional ischaemia (Ambepityia *et al*). 437 *P*
Diabetic autonomic neuropathy, and QT prolongation (Chambers *et al*). 97 *P*
Diabetic men with autonomic neuropathy, and silent ischaemia and QT prolongation (O'Sullivan *et al*). 444 *P*
Diagonal earlobe creases and fatal cardiovascular disease, necropsy study (Kirkham *et al*). 361
Digital
 computer analysis, and colour Doppler flow mapping, value in measurement of mitral regurgitation in vitro (Simpson). 106 *P*
 subtraction angiography, intravenous, in demonstration of ascending aorta in infective endocarditis. correspondence (Smyllie *et al*). 554
  coronary angiograms after PTCA comparison of analysis measurements (Katritsis *et al*). 85 *P*
Digitised M mode echocardiography in non-invasive distinction of restrictive cardiomyopathy and constrictive pericarditis (Morgan *et al*). 29
Digoxin
 effects in ventricular septal defects, and heart failure in infants (Salmon *et al*). 115 *P*
 effects of withdrawal and reintroduction in heart failure in sinus rhythm after long term treatment (Pugh *et al*) 529
Diltiazem
 in comparison of silent ischaemia after infarction and in chronic stable angina (Khan *et al*). 471 *P*
 myocardial protection, during percutaneous coronary angioplasty (Seth *et al*). 439 *P*
Disopyramide
 intravenous, versus intravenous flecainide in reversion of atrial fibrillation (Wiseman & Nathan). 470 *P*
 in termination of ventricular tachycardia comparative efficacy and safety (Griffith *et al*). 123 *P*
Distension during surgical preparation reduces short term patency in arteriovenous bypass grafting, pig (Bryan *et al*). 464 *P*
Dobutamine, and dopexamine haemodynamic effects compared in severe heart failure (Tan *et al*). 87 *P*
Dopexamine and dobutamine haemodynamic effects compared in severe heart failure (Tan *et al*). 87 *P*
Doppler
 analysis of blood flow in superior vena cava, clinical and echocardiographic correlation (Parsons *et al*). 481 *P*
 and colour flow mapping, and echocardiography, role before, during, and after mitral valve dilatation (Monaghan *et al*). 79 *P*
 technology in search of an application. review (Monaghan & Mills). 133
 continuous wave spectra, in determination of ratio of pulmonary blood flow to systemic blood flow (Jenni *et al*). 167
 diastolic indices, association with functional capacity in hypertropic cardiomyopathy (Karatasakis *et al*). 100 *P*
 echocardiography characteristics of prosthetic valves in tricuspid position (Pye *et al*). 92 *P*
  indices, left ventricular diastolic function, influence correspondence (Abinader & Sharif). 483
 use in determination of left ventricular dP/dt max (Hunt *et al*). 116 *P*
 isometric exercise in denervated heart (Robson *et al*). 224
  pulsed, left ventricular diastolic filling in cardiac amyloidosis (Kinoshita *et al*). 198
Double
 inlet ventricle and tricuspid atresia, is pulmonary artery banding obsolete (Franklin *et al*). 479 *P*
 outlet right ventricle, morphology shown by magnetic resonance imaging (Parsons *et al*). 480 *P*
  with subpulmonary ventricular septal defect, venous compared with anatomical repair (Musumeci & Lincoln). 89 *P*
dP/dt max, left ventricular, Doppler echocardiography in determination (Hunt *et al*). 116 *P*
Ductus arteriosus, percutaneous closure, severe haemolysis after: case report (Ladusans *et al*). 548
Dyspnoea on exercise in chronic heart failure, dissociated from hyperventilation (Davies *et al*). 443 *P*

Earlobe creases, diagonal, and fatal cardiovascular disease, necropsy study (Kirkham *et al*). 361
Early diastolic function, and left ventricular filling during angina in coronary artery disease (Dawson & Gibson). 248
Echocardiography and Doppler and colour flow mapping, role of before, during, and after mitral valve dilatation (Monaghan *et al*). 79 *P*
Editor, Krikler D M 3
Editorial
  Reactive oxygen metabolites and the human myocardium (Burrell & Blake). 4
  Successful and unsuccessful coronary thrombolysis (Davies) 381
  Electrical bioimpedance cardiography, in non-invasive measurement of cardiac output during myocardial infarction (Findlay *et al*). 444 *P*
  Electrocardiographic findings in male veteran endurance athletes (Northcote *et al*). 155
  Electrode catheter ablation for ventricular tachycardia, efficacy of single cathodal shock (Hauer *et al*). 38
  Enalapril effects on myocardial noradrenaline overflow during exercise in chronic heart failure (Mulligan *et al*). 23
  Endocardial fibroelastosis, severe, neonates with critical aortic stenosis, results of percutaneous balloon dilatation (Ladusans *et al*). 470 *P*
  Endocarditis in intravenous drug abusers with staphylococcal septicaemia (Burns *et al*) 356
  125$_I$-Endothelin binding sites, autoradiographic localisation, ischaemic heart disease changes (Dashwood *et al*). 440 *P*
  Enterovirus RNA in myocardium with dilated cardiomyopathy (Archard *et al*). 73 *P*
Epicardial
 approach to surgical treatment of Wolff-Parkinson-White syndrome (Ratnatunga *et al*). 462 *P*
 electrogram during successive balloon occlusion during percutaneous transluminal coronary angioplasty (Taggart *et al*). 84 *P*
 mapping, computerised intraoperative, of QRS alternans during orthodromic tachycardia, new insights (Shenasa *et al*). 96 *P*
Epidural spinal stimulation in intractable angina (Sanderson *et al*). 462 *P*
Epoprostenol infusion during coronary angioplasty, effect (Gershlick *et al*). 461 *P*
Exercise
 after heart and heart-lung transplantation (Banner *et al*). 215
 capacity, in hypertrophic cardiomyopathy, objective assessment (Frenneaux *et al*). 75 *P*
  increased, and reversal of exercise induced myocardial ischaemia in haemodialysis treated with recombinant human erythropoietin (Lewis *et al*) 436 *P*

    reduced, inefficient gait contributes to, in chronic heart failure (Davies *et al*). 437 *P*
    and symptoms in severe heart failure, effect of flosequinan (Elborn *et al*). 331
  during, and at rest, optimal atrioventricular delay, patients with dual chamber pacemakers, non-invasive assessment by continuous wave Doppler (Mehta *et al*). 161
  impaired blood pressure response to, in coronary artery disease (Okamatsu *et al*). 149
  induced non-ischaemic right ventricular tachycardias, reproducibility (Mehta *et al*). 474 *P*
  isometric, in denervated heart, Doppler echocardiographic study (Robson *et al*). 224
  pre-excitation induced, associated with anteroseptal accessory atrioventricular connections sensitive to adenosine and verapamil (Garratt *et al*). 475 *P*
  with QT shortening, influence of pacing rate (Coghlan *et al*). 469 *P*
  related paroxysmal ventricular tachycardia, role of atropine and isoprenaline (Toda *et al*) 268
  renography in heart failure (Conway *et al*) 80 *P*
  test, new, for assessment of heart failure, use of self powered treadmill (Parameshwar *et al*). 421
  testing, hypocapnia during, in dilated cardiomyopathy and hypertrophic cardiomyopathy (Moore *et al*). 435 *P*
    soon after myocardial infarction (Peart *et al*). 231
  training, effect on myocardial perfusion in angina pectoris (Todd & Ballantyne). 107 *P*

Fatigue and slow recovery in human atrioventricular node (Shenasa *et al*). 103 *P*
Felodipine as single agent in coronary artery disease, effects of treatment (Metcalfe *et al*) 258
Fetal echocardiography, diagnosis of critical aortic valve stenosis perinatal management: case report (Robertson *et al*). 365
Fibreoptic disposable catheter-tip pressure transducer of very small dimensions for cardiovascular investigations (Pappageorgio *et al*). 457 *P*
Fibrillation and ventricular tachycardia, hospital mortality (Dougeni-Christacou *et al*). 125 *P*
Filling, active, of left ventricle, evidence, study of association of ventricular torsion, and ventricular volume (Smith). 113 *P*
First pass radionuclide angiography, assessment of valvar regurgitation by new technique, whole bolus ratio (Wiseman *et al*). 465 *P*
Fitness and coronary risk factors (Davies *et al*). 444 *P*
Flecainide
  efficacy for atrial arrhythmias after open heart surgery (Wafa *et al*). 124 *P*
  intravenous, versus intravenous disopyramide in reversion of atrial fibrillation (Wiseman & Nathan). 470 *P*
  in termination of ventricular tachycardia, comparative efficacy and safety (Griffith *et al*). 123 *P*
Flosequinan effect on exercise capacity and symptoms in severe heart failure (Elborn *et al*). 331
Fontan reconstruction
  in vitro flow studies to improve hydrodynamic design (Kilner *et al*). 89 *P*
  abnormal cardiac signs after, indicators of residua and sequelae (Leung *et al*). 52
Fox K M Assistant Editor 3
Fragile X syndrome, cardiac abnormalities (Sreeram *et al*). 289
Free radical
  chronic heart failure and effect of captopril (McMurray *et al*). 457 *P*
  circulating concentrations in myocardial infarction (Higham *et al*). 454 *P*
  generation by myocardium, comparative lack during cardiac surgery (Davies *et al*). 78 *P*
  and myocardial function: editorial (Burrell & Blake) 4
Frontal plane axis significance in non-ischaemic right ventricular tachycardias (Mehta *et al*) 474 *P*

Gait, inefficient, contributes to reduced exercise capacity in chronic heart failure (Davies *et al*). 437 *P*
Glucose metabolism, and early coronary atherogenesis and myocardial infarction in Asians (Hughes *et al*). 78 *P*
Great arteries, magnetic resonance imaging, infants (Baker *et al*). 75 *P*
Growth potential of immature lung transplantation, immature rat (Hislop *et al*). 82 *P*

Haemodialysis treated with recombinant human erythropoietin, increased exercise capacity and reversal of exercise induced myocardial ischaemia (Lewis *et al*). 436 *P*
Haemolysis, severe, after percutaneous closure of ductus arteriosus: case report (Ladusans *et al*). 548
Hancock prostheses, ten year results of randomised trial (Bloomfield *et al*). 452 *P*
Heart
  attack risk, breathlessness, and lung function (Cook & Shaper). 122 *P*
  failure, atrial natriuretic factor plasma concentration increase by atriopeptidase inhibition (Northridge *et al*). 458 *P*
    captopril does not potentiate action of loop diuretics (Flapan *et al*) 87 *P*
    chronic, dyspnoea on exercise, dissociated from hyperventilation (Davies *et al*). 443 *P*
      hyperventilation response to exercise, critical level of exercise capacity determines (Davies *et al*). 436 *P*
      hypoxia, myocardial ischaemia and arrhythmias during sleep (Davies *et al*) 458 *P*
      inefficient gait contributes to reduced exercise capacity (Davies *et al*). 437 *P*
      low dose infusions of atrial natriuretic peptide, haemodynamic and renal effects (Polonia *et al*). 86 *P*
    dopexamine and dobutamine haemodynamic effects compared (Tan *et al*). 87 *P*
    and exercise renography (Conway *et al*). 80 *P*
    free radical activity and effect of captopril (McMurray *et al*) 457 *P*
    left, chronic, pulmonary capillary permeability (Davies *et al*). 477 *P*
    new exercise test for assessment, use of self powered treadmill (Parameshwar *et al*). 421
    phosphorus magnetic resonance spectroscopy of leg muscle (Arnolda *et al*). 459 *P*
    prevalence in two general practices (Parameshwar *et al*). 114 *P*
    severe, flosequinin effect on exercise capacity and symptoms (Elborn *et al*). 331
    skeletal muscle and whole body protein turnover (Morrison *et al*). 459 *P*
    and ventricular septal defects, digoxin effects, infants (Salmon *et al*). 115 *P*
  and heart-lung transplantation, in children (Radley-Smith & Yacoub). 91 *P*
    exercise after (Banner *et al*). 215
  rate variability after myocardial infarction, prognostic value (Farrell *et al*). 121 *P*
  sounds, third and fourth, relation to blood velocity during left ventricular filling (Vancheri & Gibson). 144
  transplantation in patients with present or past malignant neoplasms (Aravot *et al*). 464 *P*
Heparin
  effect on platelet thrombus deposition and vasospasm after arterial angioplasty (Penny *et al*) 117 *P*
  in myocardial infarction, reduction in major morbidity and mortality (MacMahon *et al*). 118 *P*
High
  density lipoprotein cholesterol, triglycerides, and ischaemic heart disease, reappraisal (Pocock *et al*). 106 *P*
  gain, signal averaged, electrocardiography in prediction of arrhythmias in hypertrophic cardiomyopathy (Cripps *et al*) 124 *P*
Hirudin, effect on platelet thrombus deposition and vasospasm after

  arterial angioplasty (Penny *et al*). 117 *P*
Hollow wire to facilitate percutaneous transluminal coronary angioplasty of occluded vessels (Smith *et al*). 326
Homografts, homovital aortic valve, evaluation (Aranki *et al*). 126 *P*
Hyperparathyroidism, primary, and essential hypertension association between blood pressure, left ventricular mass, and free cytosolic calcium (Dominiczak *et al*). 104 *P*
Hypertension, essential, and primary hyperparathyroidism, association between blood pressure, left ventricular mass, and free cytosolic calcium (Dominiczak *et al*). 104 *P*
Hyperventilation
  dyspnoea on exercise in chronic heart failure, dissociated from (Davies *et al*). 443 *P*
    response to exercise in chronic heart failure, critical level of exercise capacity determines (Davies *et al*). 436 *P*
  Hypocapnia during exercise testing in dilated cardiomyopathy and hypertrophic cardiomyopathy (Moore *et al*). 435 *P*
  Hypoxia during sleep in chronic heart failure (Davies *et al*). 458 *P*

Immunological marker for alcohol related myocardial disease (Cleland *et al*). 113 *P*
Impedance cardiography, pitfalls and limitations in use: correspondence (de Mey & Belz Smith) 128
Indium-111 labelled monoclonal antimyosin antibody for detection of myocardial necrosis in subendocardial infarction and unstable angina (Levy *et al*). 101 *P*
Infarct related vessel, results of successful and unsuccessful thrombolysis (Onodera *et al*). 385
Infective endocarditis
  demonstration of ascending aorta, by intravenous digital subtraction angiography: correspondence (Smyllie *et al*). 554
  precordial and transoesophageal echocardiography in spectrum, comparative value (Taams *et al*). 93 *P*
Inositol phosphate production and proto-oncogene expression in left ventricle after induction of coarctation hypertension, rat (Heagerty *et al*) 440 *P*
Insulin, high, and C-peptide concentration, associated with coronary disease, Asians (Hughes *et al*). 445 *P*
Internal mammary graft
  improved patency rates to small vessels with (Pepper *et al*). 109 *P*
  percutaneous transluminal angioplasty (Bell *et al*). 417
Intracardiac fistulas, detection by colour flow mapping after aortic valve surgery for endocarditis (Smyllie *et al*). 449 *P*
Intravascular three dimensional imaging of the arteries, novel ultrasound system (Burrell *et al*). 476 *P*
Ischaemic heart disease
  cardiac sympathetic neural activity (McCance). 105 *P*
  high density lipoprotein cholesterol, and triglycerides, reappraisal (Pocock *et al*) 106 *P*
  and noradrenaline kinetics (McCance & Forfar). 238
Ischaemia, silent and symptomatic, functional and angiographic comparison (Fox *et al*). 436 *P*
ISIS-2: large randomised trial of intravenous streptokinase and oral aspirin in acute myocardial infarction (Collins *et al*) 71 *P*
Isolated heart block, sinus of Valsalva unruptured aneurysm presenting with, echocardiographic diagnosis and successful surgical repair. case report (Ahmad *et al*) 375
Isoprenaline
  as aid to induction of catecholamine dependent supraventricular tachycardias during programmed stimulation (Brembilla-Perrot *et al*). 348
  an initiation of supraventricular tachycardia (Toda *et al*). 268

Jubilee Editorial
  A 50 year perspective: the British Heart Journal
  A title lost, but a reputation won (Krikler). 1

Kensey catheter in occlusive vascular disease (Gehani *et al*). 85 *P*
Krikler D M Editor 3

Laser
  generated tissue debris causes considerable platelet aggregation in vitro (Scriven & Nathan). 447 *P*
  thermal angioplasty, limitations in coronary circulation (Keogh *et al*). 86 *P*
    for peripheral to coronary arteries (Rosenthal *et al*) 99 *P*
  wire for percutaneous angioplasty of chronically occluded coronary arteries (Bowes *et al*). 438 *P*
Lignocaine in termination of ventricular tachycardia, comparative efficacy and safety (Griffith *et al*). 123 *P*
Lipid abnormalities influence on development of coronary arterial disease after heart transplantation (Barbir *et al*). 462 *P*
Loading conditions, effect on right ventricular pressure-volume association (Redington *et al*) 81 *P*
Lung
  function, breathlessness, and risk of heart attack (Cook & Shaper). 122 *P*
  preservation, 12 hour, deleterious effects of prostaglandin E1 (Bonser *et al*). 463 *P*
  transplantation, immature, growth potential, immature rat (Hislop *et al*). 82 *P*

Magnetic resonance imaging
  of atrioventricular septal defects correlates with echocardiographic, angiographic, and surgical findings, children (Parsons *et al*). 117 *P*
  of cardiac sarcoidosis (Underwood *et al*). 103 *P*
  chemical shift, atheroma (Mohiaddin *et al*). 119 *P*
  in double outlet right ventricle morphology (Parsons *et al*). 480 *P*
  of the great arteries in infants (Baker *et al*). 75 *P*
Magnetic resonance tagging in measurement of human left ventricular twist (Buchalter *et al*). 112 *P*
Malignant neoplasms, present or past, and heart transplantation (Aravot *et al*). 464 *P*
Microemboli and cerebral impairment during cardiac surgery, Doppler detection (Pugsley *et al*) 463 *P*
Microembolism, middle cerebral artery, bubble oxygenator with arterial line filter, and membrane oxygenator alone, compared (Griffin *et al*). 449 *P*
Microprocessor controlled current based defibrillator, initial experience (Dalzell *et al*). 502
Mills P G Assistant Editor 3
Mitral
  bioprostheses implantation, tricuspid regurgitation and pulmonary artery pressure, five years after (Ikram *et al*). 450 *P*
  prostheses with transoesophageal echocardiography, assessment (Nihoyannopoulos *et al*). 471 *P*
  regurgitation measurement in vitro, value of colour Doppler flow mapping and digital computer analysis (Simpson). 106 *P*
  stenosis, haemodynamic assessment, in presence of atrial fibrillation (Davies *et al*) 116 *P*
    inoperable, and balloon dilatation of mitral valve (Shaw *et al*). 452 *P*
    left ventricular dysfunction, possible cause by isolated posterobasal wall abnormality (Molajo *et al*). 98 *P*
    severe, decreased pulmonary microvascular permeability (Davies *et al*). 91 *P*
  valve, dilatation, echocardiography, and Doppler and colour flow mapping role, before, during, and after (Monaghan *et al*). 79 *P*
    percutaneous transluminal balloon dilatation in pregnancy: case report (Smith *et al*) 551
    prolapse and collagen genes (Henney *et al*). 292
      familial, and collagen genes (Wordsworth *et al*). 300
    repair, relative values of intra-operative epicardial and transoesophageal echocardiography (Fraser *et al*). 451 *P*
Monorail system for simple and complex percutaneous coronary angioplasty (Bergman *et al*) 447 *P*
Morquio syndrome, (mucopolysaccharidosis type IV) cardiac abnormalities (John *et al*) 450 *P*
Mortality, hospital, of ventricular tachycardia and fibrillation

  (Dougeni-Christacou *et al*). 125 *P*
Mucopolysaccharidosis, type IV, (Morquio syndrome) cardiac abnormalities (John *et al*). 450 *P*
Multiple and single vessel percutaneous transluminal coronary angioplasty in multivessel coronary artery disease, complication rates (Hunt *et al*). 440 *P*
Multivariate analysis in simplification of broad complex tachycardia diagnosis (Griffith *et al*). 475 *P*
Multivessel disease, successful percutaneous coronary angioplasty, long term clinical results after (Henderson *et al*). 438 *P*
Mustard's operation
  long term haemodynamics in symptom free children (Carvalho *et al*). 90 *P*
  for transposition of the great arteries, percutaneous balloon dilatation may relieve pulmonary venous pathway obstruction after (Sullivan *et al*). 472 *P*
Myocardial
  hypertrophy and mechanical restitution in isolated human myocardium (Cooper *et al*). 112 *P*
   ambulatory ST segment deviation after, implications for exercise ischaemia and left ventricular function (Currie & Saltissi). 454 *P*
   baroreceptor sensitivity after, correlation with electrophysiological studies (Farrell *et al*). 472 *P*
   and circulating concentrations of free radicals (Higham *et al*) 454 *P*
   during coronary artery occlusion platelets influence on extent (Chakrabarty *et al*). 78 *P*
   different variables in prediction of arrhythmic events (Cripps *et al*). 83 *P*
   and early coronary atherogenesis in Asians, and glucose metabolism (Hughes *et al*). 78 *P*
   exercise testing, soon after (Peart *et al*). 231
   and intensive approach compared with less intense management (Sanderson *et al*) 454 *P*
   see also Exercise
   heart rate variability after, prognostic value (Farrell *et al*). 121 *P*
   heparin in reduction of major morbidity and mortality (MacMahon *et al*). 118 *P*
   in infancy, unmasking anomalous origin of left coronary artery from pulmonary artery by ligation of an arterial duct. case report (Sreeram *et al*). 307
   intravenous streptokinase and oral aspirin, ISIS-2 large randomised trial (Collins *et al*). 71 *P*
   left ventricular diastolic function, pulsed Doppler assessment (Flannery *et al*). 466 *P*
   myocardium at further risk after thrombolysis (Norell *et al*). 116 *P*
   neuroendocrine responses to captopril in acute heart failure after (McAlpine *et al*). 81 *P*
   non-invasive measurement of cardiac output by electrical bioimpedance cardiography, during (Findlay *et al*). 444 *P*
   non-Q wave, characteristics and prognosis (Fox *et al*). 122 *P*
   and no specific ECG changes, favourable long term prognosis (Boden *et al*). 396
   pathological changes after intravenous streptokinase treatment (Richardson *et al*). 390
   programmed ventricular stimulation in survivors, prognostic significance (Bhandari *et al*). 410
   Q wave, do reciprocal ECG changes represent additional ischaemia or necrosis (Jain *et al*). 471 *P*
   rapid recanalisation, by serial intravenous bolus injections of recombinant tissue type plasminogen activator (Khan *et al*) 453 *P*
   reciprocal ST segment depression, diagnostic importance (Yousif *et al*). 121 *P*
   recombinant tissue plasminogen activator, double blind placebo controlled study of early and late administration (McNeill *et al*). 316
   and streptokinase for preservation of left ventricular function compared after (White *et al*) 72 *P*
   right ventricular, diagnostic accuracy of electrocardiographic right chest leads V3R to V7R, 43 consecutive fatal cases (Andersen *et al*). 514
   right ventricular dysfunction enhances mortality after (McGhie *et al*). 121 *P*
   effects of streptokinase on plasma atrial natriuretic peptide (Phillips *et al*). 139
   treated with streptokinase, coronary lesion morphology (Davies *et al*). 72 *P*
   and stroke risk factors, women in United Kingdom, assessed in general practice (Thompson *et al*). 403
   and thrombolysis, adequate provision in England questioned (Skehan *et al*). 453 *P*
   electrocardiographic evidence of myocardial salvage after (Hogg *et al*). 489
   treatment of pain: review (Herlitz *et al*). 9
   uncomplicated, prediction of outcome, 394 patients with five years follow up (Akhras & Jackson). 120 *P*
  ischaemia during sleep in chronic heart failure (Davies *et al*). 458 *P*
   reproducibility of site (Tweddel *et al*). 107 *P*
   in syndrome X, long term prognosis and variability (Pupita *et al*). 443 *P*
  necrosis in subendocardial infarction and unstable angina, indium-111 labelled monoclonal antimyosin antibody for detection (Levy *et al*). 101 *P*
  perfusion, in angina pectoris, effect of exercise training (Todd & Ballantyne). 107 *P*
   SPET scintigraphy in coronary artery disease, thallium 201 and technetium-99m MIBI compared (Mittal *et al*) 119 *P*
  protection with diltiazem during percutaneous coronary angioplasty (Seth *et al*). 439 *P*
Myocardium
  comparative lack of free radical generation during cardiac surgery (Davies *et al*). 78 *P*
  further risk after thrombolysis in acute myocardial infarction (Norell *et al*). 116 *P*
  human, and reactive oxygen metabolites: editorial (Burrell & Blake). 4

Neuroendocrine responses to captopril in acute heart failure after myocardial infarction (McAlpine *et al*). 81 *P*
Nifedipine effect on cold intolerance in angina pectoris (Peart *et al*). 521
Non-Q wave myocardial infarction, characteristics and prognosis (Fox *et al*). 122 *P*
Noradrenaline
  kinetics in ischaemic heart disease (McCance & Forfar). 238
  myocardial overflow, effects of enalapril during exercise in chronic heart failure (Mulligan *et al*). 23
  output, cardiac, during percutaneous transluminal coronary angioplasty (McCane & Forfar). 461 *P*
Notices, 130, 214, 308, 380, 484, 553

Obese subjects after weight loss, improvement of subclinical left ventricular dysfunction (DasGupta *et al*). 101 *P*
Obituary: William Evans (Evans) 68
Open heart surgery
  cardiac rehabilitation after, and return to work (Black *et al*). 448 *P*
  efficacy of flecainide for atrial arrhythmias after (Wafa *et al*). 124 *P*
Orthodromic tachycardia, new insights with computerised intraoperative epicardial mapping of QRS alternans during (Shenasa *et al*) 96 *P*
Oxygen transport monitoring in cardiogenic shock (Creamer *et al*). 445 *P*
Oxygenators compared, middle cerebral artery microembolism (Griffin *et al*). 449 *P*

Paced and natural rate response during everyday activity (Sulke *et al*). 476 *P*

Pacemakers
  atrial demand, sinus node disease paced, electrophysiological follow up (Murphy *et al*). 467 *P*
  dual chamber, importance of different atrioventricular intervals to improved exercise performance (Haskell & French). 46
    optimal atrioventricular delay at rest and during exercise, non-invasive assessment by continuous wave Doppler (Mehta *et al*). 161
  temporary, hazards associated with use before permanent pacing (Winner & Boon) 96 *P*
Pacing
  cardiac, and malignant vasovagal syndrome in 332 syncopal patients (Fitzpatrick *et al*). 97 *P*
  correcting a block, successful experience of small British pacing centre: correspondence (Joseph). 212
  endocardial, long term follow up, children of 15 kg or less (Till *et al*). 467 *P*
  rate adaptive, by ventricular depolarisation gradient as control parameter in closed loop system, clinical assessment (Paul *et al*) 469 *P*
  rate influence on QT shortening with exercise (Coghlan *et al*). 469 *P*
  wire electrode, temporary epicardial, saphenous vein graft injury during removal. case report (Price & Keenan). 546
Pain treatment in myocardial infarction: review (Herlitz *et al*). 9
Paroxysmal ventricular tachycardia, exercise related, role of atropine and isoprenaline (Toda *et al*). 268
Peptide containing neural and endocrine elements in human heart (Wharton *et al*). 112 *P*
Percutaneous angioscopy, assessment with high optical quality imaging (Rees *et al*). 86 *P*
Percutaneous transluminal coronary angioplasty
  balloon dilatation, of aortic valve, for congenital aortic stenosis in childhood (Sullivan *et al*). 186
  for critical aortic stenosis in neonates with severe endocardial fibroelastosis (Ladusans *et al*). 470 *P*
    mechanism, magnitude, and duration of effects (Rosenthal *et al*). 92 *P*
    as treatment of choice for aortic recoarctation (Sullivan *et al*). 480 *P*
    may relieve pulmonary venous pathway obstruction after Mustard's operation for transposition of the great arteries (Sullivan *et al*). 472 *P*
    measurement of inflated size during percutaneous coronary angioplasty (Penny *et al*). 447 *P*
  of mitral valve by double and single balloon techniques (Jewitt *et al*). 91 *P*
    in pregnancy: case report (Smith *et al*). 551
    "inoperable" mitral stenosis (Shaw *et al*). 452 *P*
  of pulmonary outflow tract as palliation of tetralogy of Fallot (Qureshi *et al*). 482 *P*
    for pulmonary stenosis, critical neonates and infants (Walsh *et al*). 77 *P*
    of stenosed bioprosthesis in tricuspid valve position: case report (Wren & Hunter). 65
  of stenosed Blalock-Taussig shunts (Qureshi *et al*). 432
  for systemic venous obstruction after Mustard's operation (Carvalho *et al*). 90 *P*
  of bifurcation lesions in major coronary vessels (Bergman *et al*). 84 *P*
  cardiac noradrenaline output during (McCance & Forfar). 461 *P*
  in chronic total occlusions, long term follow up after (Nouriel *et al*). 94 *P*
  lesions effect on results (Balcon *et al*). 446 *P*
Percutaneous transluminal coronary angioplasty, dynamic, normal and abnormal coronary arteries (Gehani *et al*). 85 *P*
  epicardial electrogram during successive balloon occlusion during (Taggart *et al*). 84 *P*
  exercise testing and prediction of restenosis after (El-Tamimi *et al*). 95 *P*
  failed, emergency operation after, how late (O'Kane *et al*). 93 *P*
  importance of procedural factors in development of recurrent restenosis (Glazier *et al*) 94 *P*
  inflated balloon size measurement during (Penny *et al*). 447 *P*
  laser wire for, in chronically occluded coronary arteries (Bowes *et al*). 438 *P*
  left internal mammary artery grafts (Bell *et al*). 417
  and left ventricular function in single vessel coronary artery disease (Najm *et al*). 262
  management and outcome of recurrent restenosis after (Glazier *et al*). 95 *P*
  in multivessel disease, complete/incomplete revascularisation compared (Seth *et al*). 79 *P*
  myocardial protection with diltiazem during (Seth *et al*). 439 *P*
Angioplasty, platelet function transcardiac changes before and after (Gershlick *et al*). 83 *P*
  results assessment from digital subtraction, comparison of methods (Katritsis *et al*). 85 *P*
  simple and complex, with Monorail system (Bergman *et al*). 447 *P*
  for single vessel disease, long term clinical follow up after (Henderson *et al*). 95 *P*
  see also Balloon dilatation
  successful, in multivessel disease, long term clinical results after (Henderson *et al*). 438 *P*
  recurrent restenosis after, outcome (Glazier *et al*). 485
  and restenosis, paradox of optimal improvement in stenosis (Beatt *et al*). 439 *P*
Perfusion, normal and ischaemic, cardiac hypertrophy effects on cellular electrophysiology (Winterton *et al*). 442 *P*
Peripheral vascular response, abnormal, in hypertrophic cardiomyopathy in relation to clinical and prognostic features (Counihan *et al*). 456 *P*
Phase analysis, quantitative, in assessment of coronary artery disease (Underwood *et al*). 14
Phosphorus
  magnetic resonance spectroscopy of leg muscle in heart failure (Arnolda *et al*). 459 *P*
  metabolism non-invasive measurement in human heart during exercise by phosphorus-31 magnetic resonance spectroscopy (Conway *et al*). 104 *P*
Phrenic nerve paralysis, frequency after cardiac surgery in children (Mok *et al*). 99 *P*
Plasminogen activator
  low dose tissue, inhibition of coronary thrombosis (Fox *et al*). 73 *P*
  recombinant tissue, and thrombolysis (Wilcox *et al*). 71 *P*
    and streptokinase compared, for left ventricular function preservation after myocardial infarction (White *et al*). 72 *P*
Platelet
  aggregation in vitro, considerable, caused by laser-generated tissue debris (Scriven & Nathan). 447 *P*
  function changes, and epoprostenol infusion (Gershlick *et al*). 461 *P*
      transcardiac, before and after angioplasty (Gershlick *et al*). 83 *P*
  influence on extent of myocardial infarction during coronary artery occlusion (Chakrabarty *et al*) 78 *P*
  thrombus deposition and vasospasm after arterial angioplasty, effects of thrombin inhibition by heparin or hirudin (Penny *et al*). 117 *P*
Posterobasal wall abnormality, isolated, possible cause of left ventricular dysfunction in mitral stenosis (Molajo *et al*). 98 *P*
Potassium, extracellular, accumulation rate, effects of sotalol (Hicks & Cobbe). 442 *P*
Precordial and transoesophageal echocardiography, in spectrum of infective endocarditis, comparative value (Taams *et al*). 93 *P*
Pre-excitation
  induced by exercise, association with anteroseptal accessory atrioventricular connections sensitive to adenosine and verapamil (Garratt *et al*). 475 *P*
  induced by respiration, autonomic regulation (Butrous *et al*). 473 *P*
  latent, unmasking, adenosine and vagal manoeuvres in sinus

  rhythm (Garratt *et al*). 467 *P*
Pregnancy, percutaneous transluminal balloon dilatation of mitral valve: case report (Smith *et al*). 551
Pressure half time in aortic regurgitation (Samstad *et al*). 336
Proceedings, British Cardiac Society, autumn meeting, London 22 to 24 November 1988, 71
  68th Annual General Meeting, Oxford, 6 and 7 April 1989, 435
Propranolol
  effect on cold intolerance in angina pectoris (Peart *et al*). 521
  induced bradycardia in tetralogy of Fallot: case report (Clark *et al*). 378
Prostaglandin E1 in 12 hour lung preservation, deleterious effects (Bonser *et al*). 463 *P*
Prosthetic valves in tricuspid position, Doppler echocardiographic characteristics (Pye *et al*). 92 *P*
Protein turnover, whole body, and skeletal muscle in heart failure (Morrison *et al*). 459 *P*
Proto-oncogene expression, myocardial, and effects of thyroid state (Gammage *et al*). 441 *P*
Pseudoaneurysm, left ventricular, colour flow imaging advantages in diagnosis (Sutherland *et al*). 59; 81 *P*
Pulmonary
  artery banding, is it obsolete for double inlet ventricle and tricuspid atresia (Franklin *et al*) 479 *P*
  pressure, and tricuspid regurgitation, five years after mitral bioprostheses implantation (Ikram *et al*). 450 *P*
  capillary permeability in chronic left heart failure (Davies *et al*) 477 *P*
  microvascular permeability, decreased, in severe mitral stenosis (Davies *et al*) 91 *P*
  stenosis, critical, percutaneous balloon dilatation, neonates and infants (Walsh *et al*). 77 *P*
  wedge pressure as good index of intra-operative myocardial ischaemia (van Daele *et al*). 477 *P*
Pulsed Doppler assessment, left ventricular diastolic function in myocardial infarction (Flannery *et al*). 466 *P*

QRS alternans, new insights with computerised intraoperative epicardial mapping, during orthodromic tachycardia (Shenasa *et al*). 96 *P*
QT
  interval in atrial fibrillation (Pai & Rawles). 510
  prolongation, in diabetic autonomic neuropathy (Chambers *et al*). 97 *P*
    and silent ischaemia, diabetic men with autonomic neuropathy (O'Sullivan *et al*). 444 *P*
  shortening with exercise, influence of pacing rate (Coghlan *et al*) 469 *P*

Radiotherapy, coronary ostial stenosis after, angioplasty or coronary artery surgery: case report (Handler *et al*). 208
Rate adaptive pacing by ventricular depolarisation gradient as control parameter in closed loop system, clinical assessment (Paul *et al*). 469 *P*
Reactive oxygen metabolites and human myocardium editorial (Burrell & Blake). 4
Reciprocal ST segment depression in myocardial infarction, diagnostic importance (Yousif *et al*). 121 *P*
Recombinant
  human erythropoietin treated haemodialysis, increased exercise capacity and reversal of exercise induced myocardial ischaemia (Lewis *et al*). 436 *P*
  tissue plasminogen activator in myocardial infarction, double blind placebo controlled study of early and late administration (McNeill *et al*). 316
Renography, exercise, in heart failure (Conway *et al*). 80 *P*
Respiration, pre-excitation induced, autonomic regulation (Butrous *et al*) 473 *P*
Restenosis
  after percutaneous transluminal coronary angioplasty, exercise testing and prediction of (El-Tamimi *et al*). 95 *P*
  recurrent, development, importance of procedural factors after PTCA (Glazier *et al*). 94 *P*
  management and outcome after PTCA (Glazier *et al*). 95 *P*
  after percutaneous transluminal balloon angioplasty, outcome (Glazier *et al*) 485
Risk factors, coronary, and fitness (Davies *et al*). 444 *P*
Rose angina questionnaire, using (Cook & Shaper). 114 *P*

Saccular aneurysm of coronary artery in association with unstable angina, serial angiographic findings during development: case report (Goudevenos *et al*). 372
Salbutamol, intracoronary injections show beta$_2$ adrenoreceptor mediated activity (Hall *et al*). 108 *P*
Saphenous vein
  graft injury during removal of temporary epicardial pacing wire electrode: case report (Price & Keenan). 546
  human, intimal proliferation in organ culture (Angelini *et al*). 108 *P*
Sarcoidosis, cardiac, magnetic resonance imaging (Underwood *et al*). 103 *P*
Schoonmaker catheter, clinical experience (Skehan *et al*). 108 *P*
Signal averaged electrocardiograms, and myocardial biopsy specimens compared in ventricular tachycardia associated with no obvious cardiac abnormality (Mehta *et al*) 102 *P*
Silent ischaemia
  exertional evidence, perception of angina in diabetes (Ambepitiya *et al*). 437 *P*
  frequency in coronary artery disease and angina receiving standard medical treatment (Mulcahy *et al*) 445 *P*
  after infarction and in chronic stable angina, compared, effect of diltiazem (Khan *et al*). 471 *P*
  myocardial, in patients referred for coronary bypass surgery because of angina, compared with those well-controlled on medical treatment (Mulcahy *et al*) 496
  and QT prolongation, diabetic men with autonomic neuropathy (O'Sullivan *et al*) 444 *P*
  and symptomatic, functional and angiographic comparison (Fox *et al*). 436 *P*
Simpson's rule in determination of left ventricular volumes in congenital heart disease, infants and children (Ino *et al*). 182
Single vessel disease, long term clinical follow up after PTCA (Henderson *et al*). 95 *P*
Sinus
  arrhythmia in atrial septal defect, children, analysis of heart rate variability before and after surgical repair (Finley *et al*) 280
  node disease paced with atrial demand pacemakers, electrophysiological follow up (Murphy *et al*). 467 *P*
  of Valsalva unruptured aneurysm presenting with isolated heart block, echocardiographic diagnosis and successful surgical repair; case report (Ahmad *et al*). 375
  venous atrial septal defect, investigation and repair (Brooks *et al*) 89 *P*
Skeletal muscle and whole body protein turnover in heart failure (Morrison *et al*) 459 *P*
Socioenvironmental factors, unemployment, and coronary heart disease, Scotland (Crombie *et al*). 172
Sotalol
  effects accumulation rate of extracellular potassium (Hicks & Cobbe). 442 *P*
  in termination of ventricular tachycardia, comparative efficacy and safety (Griffith *et al*). 123 *P*
Staphylococcal septicaemia, endocarditis in intravenous drug abusers with (Burns *et al*). 356
Stenosed bioprosthesis percutaneous balloon dilatation in tricuspid valve position: case report (Wren & Hunter). 65
Stenosis
  paradox of optimal improvement, by percutaneous transluminal coronary angioplasty and restenosis (Beatt *et al*) 439 *P*
  severity, arteriographic underestimations of vessel diameter lead-

  ing to overestimation (Pappageorgio *et al*). 478 *P*
  Stent implantation for coronary artery bypass graft stenosis treatment (Beatt *et al*). 446 *P*
  Streptokinase
  effects on plasma atrial natriuretic peptide in myocardial infarction (Phillips *et al*). 139
  intravenous, and oral aspirin in acute myocardial infarction, ISIS-2, large randomised trial (Collins *et al*). 71 *P*
  and recombinant tissue plasminogen activator compared for left ventricular function preservation after myocardial infarction (White *et al*). 72 *P*
  intravenous, in myocardial infarction, pathological changes after (Richardson *et al*). 390
  for myocardial infarction, coronary lesion morphology (Davies *et al*). 72 *P*
Stress
  response of flow and distribution, in normal coronary arteries (Tweddel *et al*). 476 *P*
  testing, district audit (Robson *et al*). 98 *P*
Stroke and myocardial infarction risk factors, women in United Kingdom, assessed in general practice (Thompson *et al*). 403
Subpulmonary ventricular septal defect with double outlet right ventricle, venous compared with anatomical repair (Musumeci & Lincoln). 89 *P*
Substance P in vivo, atherosclerotic human coronary vessels preserve dilator response to (Crossman *et al*). 455 *P*
Superior vena cava, Doppler analysis of blood flow, clinical and echocardiographic correlation (Parsons *et al*). 481 *P*
Supravalvar aortic stenosis, symmetrical aortoplasty repair (Angelini *et al*). 482 *P*
Supraventricular tachycardias
  catecholamine dependent, isoprenaline as aid to induction during programmed stimulation (Brembilla-Perrot *et al*) 348
  verapamil or adenosine (Rankin *et al*). 123 *P*
Sympathetic
  neural activity, cardiac, in ischaemic heart disease (McCance). 105 *P*
  neurohormonal response to dynamic exercise early after orthotopic cardiac transplantation (Banner *et al*). 127 *P*
Syndrome X
  abnormal left ventricular filling during dipyridamole echocardiography (Nadazdin *et al*). 478 *P*
  and myocardial ischaemia, long term prognosis and variability (Pupita *et al*) 443 *P*
  as a variable degree of myopathy (Tweddel *et al*). 74 *P*
Systemic lupus erythematosus, cardiac abnormalities, association with raised cardiolipin antibodies (Gomez *et al*). 80 *P*

Tachycardia
  broad complex, simplification of diagnosis by multivariate analysis (Griffith *et al*). 475 *P*
  initiation and termination windows, reproducible in long term (Bucknall *et al*). 468 *P*
Technetium-99 MIBI and thallium 201 compared in myocardial perfusion SPET scintigraphy in coronary artery disease (Mittal *et al*). 119 *P*
Temperature effect on rate of left ventricular pressure fall, humans (Luke *et al*). 426
Tetralogy of Fallot
  efficacy of palliation by percutaneous balloon dilatation of pulmonary outflow tract (Qureshi *et al*). 482 *P*
  propranolol induced bradycardia: case report (Clark *et al*). 378
  total correction, assessment of survival (Ladusans *et al*). 90 *P*
Thallium 201 and technetium-99 MIBI compared in myocardial perfusion SPET scintigraphy in coronary artery disease (Mittal *et al*). 119*P*
Thoracic aortic dissection, acute, suspected, aortography and computed tomographic scanning (Morgan *et al*) 466 *P*
Thrombolysis
  in cardiogenic shock (Burke *et al*). 88 *P*
  comparison of recombinant tissue plasminogen activator and streptokinase after myocardial infarction (White *et al*). 72 *P*
  coronary lesions after, irregularity predicts need for urgent intervention (Davies *et al*). 452 *P*
  coronary, successful and unsuccessful: editorial (Davies). 381
  direct admission to coronary care unit (Burns *et al*). 322
  for myocardial infarction, adequate provision in England questioned (Skehan *et al*). 453 *P*
    electrocardiographic evidence of myocardial salvage after (Hogg *et al*). 489
  one year mortality, home/coronary care unit treatment compared (Burke *et al*). 72 *P*
  with recombinant tissue plasminogen activator (rt-PA) (Wilcox *et al*). 71 *P*
  successful and unsuccessful, features of infarct related vessel (Onodera *et al*). 385
  see also Plasminogen: Streptokinase
Thyroid state, and myocardial proto-oncogene expression (Gammage *et al*). 441 *P*
Transmitral velocities measured by pulsed Doppler in healthy volunteers, effects of acute changes in blood pressure and heart rate (Smith *et al*). 344
Transoesophageal
  approach to defibrillation of ventricular fibrillation (McKeown *et al*). 468 *P*
  DC cardioversion (McKeown *et al*). 96 *P*
  echocardiography, improved diagnostic technique for subaortic membranes (Sutherland *et al*). 76 *P*
    method of choice to visualise left atrial pathology (de Belder *et al*). 478 *P*
    with mitral prostheses, assessment (Nihoyannopoulos *et al*). 471 *P*
    outpatient, technique, patient tolerance, and costs (Leech *et al*). 479 *P*
    role in diagnosis of aortic dissection, cooperative multicentre trial (Sutherland *et al*). 125 *P*
    value in congenital heart disease, adolescents and adults (Sutherland *et al*). 480 *P*
    and precordial, in spectrum of infective endocarditis, comparative value (Tams *et al*) 93 *P*
Transplantation, orthotopic, sympathetic neurohormonal response to dynamic exercise early after (Banner *et al*) 127 *P*
Transvenous His bundle ablation, short term and long term, prediction of success (Agarwal & Redding). 99 *P*
Tricuspid
  atresia, and double inlet ventricle, is pulmonary artery banding obsolete (Franklin *et al*). 479 *P*
  regurgitation and pulmonary artery pressure, five years after mitral bioprostheses implantation (Ikram *et al*). 450 *P*
Triglycerides, ischaemic heart disease, and high density lipoprotein cholesterol, reappraisal (Pocock *et al*). 106 *P*

Ultrasound, intravascular three dimensional imaging of the arteries (Burrell *et al*). 476 *P*
Unemployment, socioenvironmental factors, and coronary heart disease, Scotland (Crombie *et al*). 172

Vagal manoeuvres during sinus rhythm and latent pre-excitation (Garratt *et al*) 467 *P*
Valvar regurgitation from first pass radionuclide angiography, whole bolus ratio, new technique for assessing (Wiseman *et al*). 465 *P*
Vasodilator response, abnormal, in hypertrophic cardiomyopathy, evidence for (Frenneaux *et al*). 74 *P*
Vasovagal syndrome, malignant, incidence in 332 syncopal patients, results of cardiac pacing (Fitzpatrick *et al*) 97 *P*
Ventricle (ventricular)
  arrhythmias pathogenesis, role of wall stress (James). 105 *P*
    prevalence in left ventricular hypertrophy caused by aortic

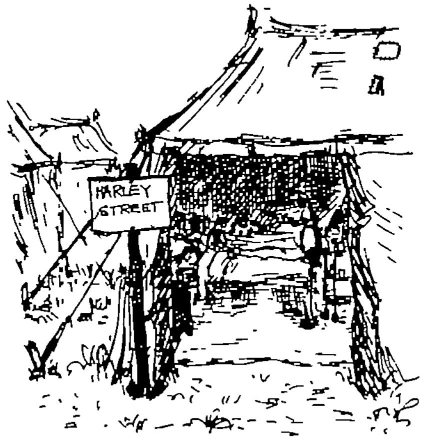
  valve disease (Al-Riyami *et al*). 450 *P*
depolarisation gradient as control parameter in closed loop system, clinical assessment of rate adaptive pacing (Paul *et al*). 469 *P*
fibrillation, transoesophageal approach to defibrillation (McKeown *et al*). 468 *P*
left, apical aneurysm, associated with sustained uniform ventricular tachycardia in hypertrophic cardiomyopathy (Alfonso *et al*). 178
  assist devices, implantable, medium term cardiovascular effects, calf (Withington *et al*). 464 *P*
  diastolic function in myocardial infarction, pulsed Doppler assessment (Flannery *et al*). 466 *P*
  dysfunction in mitral stenosis, possible cause by isolated posterobasal wall abnormality (Molajo *et al*). 98 *P*
    subclinical, improvement in obese subjects after weight loss (DasGupta *et al*) 101 *P*
  filling, active, evidence study of association of ventricular torsion, and ventricular volume (Smith) 113 *P*
    diastolic, impaired, in familial amyloid polyneuropathy, pulsed Doppler echocardiographic study (Kinoshita *et al*) 198
    and early diastolic function during angina in coronary artery disease (Dawson & Gibson). 248
    relation of third and fourth heart sounds to blood velocity during (Vancheri & Gibson). 144
    Cardioscint, new system for continuous evaluation (Lahiri *et al*). 102 *P*
    continuous monitoring by Cardioscint, validation (Broadhurst *et al*) 465 *P*
    late, after anatomical correction of anomalous left coronary artery (Kirk *et al*) 110 *P*
    and percutaneous transluminal coronary angioplasty in single vessel coronary artery disease (Najm *et al*) 262
  hypertrophy caused by aortic valve disease, prevalence of ventricular arrhythmias (Al-Riyami *et al*). 450 *P*
  pressure fall rate, effect of temperature, humans (Luke *et al*). 426
  pseudoaneurysm, colour flow imaging advantages in diagnosis (Sutherland *et al*). 59; 81 *P*
  twist, human, measurement by magnetic resonance tagging (Buchalter *et al*). 112 *P*
  volumes determination by Simpson's rule in congenital heart disease, infants and children (Ino *et al*) 182
paced evoked response, electrophysiological basis of configurations (Baig *et al*). 473 *P*
right, dysfunction enhances mortality after myocardial infarction (McGhie *et al*) 121 *P*
  infarction, diagnostic accuracy of electrocardiographic right chest leads V3R to V7R, 43 consecutive fatal cases (Andersen *et al*). 514
  pressure-volume association, effect of loading conditions (Redington *et al*). 81 *P*
  tachycardias, non-ischaemic, reproducibility, induced by exercise (Mehta *et al*). 474 *P*
    non-ischaemic, significance of frontal plane axis (Mehta *et al*). 474 *P*
septal defects, colour flow mapping as intraoperative angiography, advantages and pitfalls (Sutherland *et al*). 127 *P*
  and heart failure, digoxin effects, infants (Salmon *et al*) 115 *P*
    post-infarct, range of coronary artery lesions and requirements for coronary arteriography (Smyllie *et al*). 114 *P*
stimulation in survivors of myocardial infarction, prognostic significance (Bhandari *et al*). 410
stroke work loss, alternative method of quantifying aortic stenosis severity (Sprigings *et al*). 451 *P*
tachycardia, adenosine, lignocaine, disopyramide, flecainide, and sotalol, comparative efficacy and safety in termination (Griffith *et al*). 123 *P*
  associated with no obvious cardiac abnormality, signal averaged electrocardiograms, and myocardial biopsy specimens compared (Mehta *et al*). 102 *P*
  electrode catheter ablation for, efficacy of single cathodal shock (Hauer *et al*). 38
  and fibrillation, hospital mortality (Dougeni-Christacou *et al*). 125 *P*
  and hypertrophic cardiomyopathy, long term survival with amiodarone (McKenna *et al*). 472 *P*
  presentation, children (Priestley *et al*). 77 *P*
  sustained uniform, in hypertrophic cardiomyopathy, associated with left ventricular apical aneurysm (Alfonso *et al*). 178
  treatment, usefulness of haemodynamic changes during (Davies *et al*). 466 *P*
topology in atrioventricular septal defect cross sectional echocardiography for recognition (Carvalho *et al*) 285
torsion and ventricular volume, in association in active filling of left ventricle (Smith). 113 *P*
Verapamil or adenosine for supraventricular tachycardia (Rankin *et al*). 123 *P*
  effect on pre-excitation induced by exercise (Garratt *et al*). 475 *P*

Wall stress, role in pathogenesis of ventricular arrhythmia (James). 105 *P*
Whole bolus ratio, new technique for assessing valvar regurgitation from first pass radionuclide angiography (Wiseman *et al*). 465 *P*
Wolff-Parkinson-White syndrome
  epicardial approach to surgical treatment (Ratnatunga *et al*). 462 *P*
  after heart transplantation: case report (Goy *et al*). 368

Blood, Sweat, and Cheers

BY SIR IAN FRASER

In the *Blood, Sweat, and Cheers* of a surgeon's life the blood needs no explanation; the sweat is the hard work; the cheers are the satisfactions of getting good results. For Ian Fraser the sweat was increased as much of his early surgery was performed in the heat of battle in the second world war; and the cheers come also from his capacity to enjoy himself in almost any circumstances.



Former president both of the Royal College of Surgeons in Ireland and of the British Medical Association, Sir Ian Fraser is eminent in his profession, but his book is not about being eminent, it is about life and its pleasures and pains, told with zest and humour and delightfully pictured in Ghislaine Howard's illustrations.

Price: Inland £14.95; Abroad £17.50;
BMA members: Inland £13.95; Abroad £16.50;
including postage, by air abroad

The
MEMOIR
Club

The BMJ's series of books of general interest by medical writers

ORDER FORM

BRITISH MEDICAL JOURNAL
PO BOX 295, LONDON WC1H 9TE
or any leading medical bookseller

Please send me

	UK	ABROAD
☐ **Blood, Sweat and Cheers** by Sir Ian Fraser	£14 95	£17.50
☐ **Reap a Destiny** by Douglas Swinscow	£14 95	£17.50
☐ **A Natural History of Everyday Life** by Lord Taylor of Harlow	£19.95	£24.00
☐ **Portraits from Memory** by Sir James Howie	£14.95	£17 50
☐ **Not Always on the Level** by E J Moran Campbell	£14.95	£18.50
☐ **Recollections and Reflections** by Sir Douglas Black	£14.95	£17.50
☐ **Doctors in Science and Society** by Sir Christopher Booth	£14.95	£19.50
BMA members please deduct from the price of Memoir Club books	£1.00	£1.00

NAME ....
Please print name and address clearly

ADDRESS ....

....

....

I enclose ....

BMA Membership No ....

Please make cheques payable to **British Medical Journal** or debit my credit card (*please tick box*)

☐ Access/MasterCard ☐ Barclaycard/Visa ☐ American Express

Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Card expiry date ....

Signature ....

☐ Please send me a book catalogue

BRITISH
HEART JOURNAL

Volume 61
1989

BRITISH MEDICAL ASSOCIATION · TAVISTOCK SQUARE · LONDON WC1H 9JR

EDITOR
DENNIS KRIKLER

ASSISTANT EDITORS
M J Davies
Kim Fox
Peter Mills

EDITORIAL COMMITTEE
(Appointed by The British Cardiac Society)

Clive P Aber
Kate Bull
Keith Dawkins
Alan B Houston
Barry R Keeton

Michael Marmot
Alexander L Muir
Paul J Oldershaw
Philip A Poole-Wilson

David B Shaw
Tom Treasure
David E Ward
John Watkins
Peter Wilde

EDITOR, *British Medical Journal*

EDITOR, *Cardiovascular Research*

TECHNICAL EDITOR
Jane Dawson

EDITORIAL ASSISTANT
Anne Oliver

STATISTICAL ADVISER
Stephen J W Evans

CONTENTS OF VOLUME 61

Number 1

JUBILEE EDITORIAL: A 50 YEAR PERSPECTIVE: THE BRITISH HEART JOURNAL D Krikler 1

EDITORIAL: REACTIVE OXYGEN METABOLITES AND THE HUMAN MYOCARDIUM C J Burrell, D R Blake 4

REVIEW: TREATMENT OF PAIN IN ACUTE MYOCARDIAL INFARCTION J Herlitz, Å Hjalmarson, F Waagstein 9

QUANTITATIVE PHASE ANALYSIS IN THE ASSESSMENT OF CORONARY ARTERY DISEASE S R Underwood, S Walton, P J Laming, P J Ell, R W Emanuel, R H Swanton 14

EFFECTS OF ENALAPRIL ON MYOCARDIAL NORADRENALINE OVERFLOW DURING EXERCISE IN PATIENTS WITH CHRONIC HEART FAILURE I P Mulligan, A G Fraser, M J Lewis, A H Henderson 23

RESTRICTIVE CARDIOMYOPATHY AND CONSTRICTIVE PERICARDITIS: NON-INVASIVE DISTINCTION BY DIGITISED M MODE ECHOCARDIOGRAPHY J M Morgan, L Raposo, J C Clague, W H Chow, P J Oldershaw 29

ELECTRODE CATHETER ABLATION FOR VENTRICULAR TACHYCARDIA: EFFICACY OF A SINGLE CATHODAL SHOCK R N W Hauer, E O Robles de Medina, P J Kuijer, P W Westerhof 38

PHYSIOLOGICAL IMPORTANCE OF DIFFERENT ATRIOVENTRICULAR INTERVALS TO IMPROVED EXERCISE PERFORMANCE IN PATIENTS WITH DUAL CHAMBER PACEMAKERS R J Haskell, W J French 46

ABNORMAL CARDIAC SIGNS AFTER FONTAN TYPE OF OPERATION: INDICATORS OF RESIDUA AND SEQUELAE M P Leung, L N Benson, J F Smallhorn, W G Williams, G A Trusler, R M Freedom 52

ADVANTAGES OF COLOUR FLOW IMAGING IN THE DIAGNOSIS OF LEFT VENTRICULAR PSEUDOANEURYSM G R Sutherland, J H Smyllie, J R T C Roelandt 59

CASE REPORT

BALLOON DILATATION OF A STENOSED BIOPROSTHESIS IN THE TRICUSPID VALVE POSITION C Wren, S Hunter 65

OBITUARY

William Evans 68

PROCEEDINGS OF THE BRITISH CARDIAC SOCIETY 71

CORRESPONDENCE 128

NOTICES 130

AUTHORS' CHECKLIST FOR MANUSCRIPTS 131

Number 2

REVIEW: DOPPLER COLOUR FLOW MAPPING: TECHNOLOGY IN SEARCH OF AN APPLICATION? M J Monaghan, P Mills 133

PLASMA ATRIAL NATRIURETIC PEPTIDE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION: EFFECTS OF STREPTOKINASE P A Phillips, J Sasadeus, G P Hodsman, J Horowitz, A Saltups, C I Johnston 139

RELATION OF THIRD AND FOURTH HEART SOUNDS TO BLOOD VELOCITY DURING LEFT VENTRICULAR FILLING F Vancheri, D Gibson 144

IMPAIRED BLOOD PRESSURE RESPONSE TO EXERCISE IN PATIENTS WITH CORONARY ARTERY DISEASE: POSSIBLE CONTRIBUTION OF ATTENUATED REFLEX VASOCONSTRICTION IN NON-EXERCISING MUSCLES S Okamatsu, A Takeshita, M Nakamura 149

ELECTROCARDIOGRAPHIC FINDINGS IN MALE VETERAN ENDURANCE ATHLETES R J Northcote, G P Canning, D Ballantyne 155

OPTIMAL ATRIOVENTRICULAR DELAY AT REST AND DURING EXERCISE IN PATIENTS WITH DUAL CHAMBER PACEMAKERS: A NON-INVASIVE ASSESSMENT BY CONTINUOUS WAVE DOPPLER
D Mehta, S Gilmour, D E Ward, A J Camm 161

DETERMINATION OF THE RATIO OF PULMONARY BLOOD FLOW TO SYSTEMIC BLOOD FLOW BY DERIVATION OF AMPLITUDE WEIGHTED MEAN VELOCITY FROM CONTINUOUS WAVE DOPPLER SPECTRA
R Jenni, M Ritter, A Vieli, H O Hirzel, E R Schmid, J Grimm, M Turina 167

UNEMPLOYMENT, SOCIOENVIRONMENTAL FACTORS, AND CORONARY HEART DISEASE IN SCOTLAND
I K Crombie, M B Kenicer, W C S Smith, H D Tunstall-Pedoe 172

CLINICAL SUSTAINED UNIFORM VENTRICULAR TACHYCARDIA IN HYPERTROPHIC CARDIOMYOPATHY: ASSOCIATION WITH LEFT VENTRICULAR APICAL ANEURYSM
F Alfonso, M P Frenneaux, W J McKenna 178

DETERMINATION OF LEFT VENTRICULAR VOLUMES BY SIMPSON'S RULE IN INFANTS AND CHILDREN WITH CONGENITAL HEART DISEASE T Ino, L N Benson, H Mikalian, R M Freedom, R D Rowe 182

BALLOON DILATATION OF THE AORTIC VALVE FOR CONGENITAL AORTIC STENOSIS IN CHILDHOOD
I D Sullivan, C Wren, H Bain, S Hunter, P G Rees, J F N Taylor, C Bull, J E Deanfield 186

DISTINGUISHING BETWEEN ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY TRUNK AND DILATED CARDIOMYOPATHY: ROLE OF ECHOCARDIOGRAPHIC MEASUREMENT OF THE RIGHT CORONARY ARTERY DIAMETER K Koike, N N Musewe, J F Smallhorn, R M Freedom 192

IMPAIRED LEFT VENTRICULAR DIASTOLIC FILLING IN PATIENTS WITH FAMILIAL AMYLOID POLYNEUROPATHY: A PULSED DOPPLER ECHOCARDIOGRAPHIC STUDY
O Kinoshita, M Hongo, H Yamada, T Misawa, J Kono, S Okubo, S-I Ikeda 198

FAMILIAL AORTIC DISSECTION: A REPORT OF RARE FAMILY CLUSTER M Toyama, A Amano, T Kameda 204

CASE REPORT

CORONARY OSTIAL STENOSIS AFTER RADIOTHERAPY: ANGIOPLASTY OR CORONARY ARTERY SURGERY?
C E Handler, S Livesey, P A Lawton 208

CORRESPONDENCE 212

NOTICES 214

Number 3

CARDIOPULMONARY RESPONSE TO DYNAMIC EXERCISE AFTER HEART AND COMBINED HEART-LUNG TRANSPLANTATION N R Banner, M H Lloyd, R D Hamilton, J A Innes, A Guz, M H Yacoub 215

ISOMETRIC EXERCISE IN THE DENERVATED HEART: A DOPPLER ECHOCARDIOGRAPHIC STUDY
S C Robson, S S Furniss, A Heads, R J Boys, C McGregor, R S Bexton 224

EXERCISE TESTING SOON AFTER MYOCARDIAL INFARCTION: ITS RELATION TO COURSE AND OUTCOME AT ONE YEAR IN PATIENTS AGED LESS THAN 55 YEARS
I Peart, O Odemuyiwa, C Albers, A Hall, C Kelly, R J C Hall 231

CARDIAC AND WHOLE BODY [^{3}H]NORADRENALINE KINETICS IN ISCHAEMIC HEART DISEASE: CONTRAST BETWEEN UNSTABLE ANGINAL SYNDROMES AND PACING INDUCED ISCHAEMIA
A J McCance, J C Forfar 238

LEFT VENTRICULAR FILLING AND EARLY DIASTOLIC FUNCTION AT REST AND DURING ANGINA IN PATIENTS WITH CORONARY ARTERY DISEASE J R Dawson, D G Gibson 248

THE EFFECTS OF TREATMENT WITH FELODIPINE AS A SINGLE AGENT IN CORONARY ARTERY DISEASE
M J Metcalfe, N S Chan-Wah-Hak, K Jennings 258

CORONARY ANGIOPLASTY AND LEFT VENTRICULAR FUNCTION IN SINGLE VESSEL CORONARY ARTERY DISEASE
Y C Najm, A D Timmis, M N Maisey, L M Y Pinies, A Salinas, P V L Curry, E Sowton 262

ELECTROPHYSIOLOGICAL STUDY OF YOUNG PATIENTS WITH EXERCISE RELATED PAROXYSMS OF PALPITATION: ROLE OF ATROPINE AND ISOPRENALINE FOR INITIATION OF SUPRAVENTRICULAR TACHYCARDIA
I Toda, T Kawahara, Y Murakawa, A Nozaki, K Kawakubo, H Inoue, T Sugimoto 268

ELECTROCARDIOGRAPHIC FINDINGS AND FREQUENCY OF ARRHYTHMIAS IN BARTTER'S SYNDROME
C Blomström-Lundqvist, K Caidahl, S B Olsson, A Rudin 274

SINUS ARRHYTHMIA IN CHILDREN WITH ATRIAL SEPTAL DEFECT: AN ANALYSIS OF HEART RATE VARIABILITY BEFORE AND AFTER SURGICAL REPAIR
J P Finley, S T Nugent, W Hellenbrand, M Craig, D A Gillis 280

CROSS SECTIONAL ECHOCARDIOGRAPHY FOR RECOGNITION OF VENTRICULAR TOPOLOGY IN ATRIOVENTRICULAR SEPTAL DEFECT J S Carvalho, M L Rigby, E A Shinebourne, R H Anderson 285

CARDIAC ABNORMALITIES IN THE FRAGILE X SYNDROME
N Sreeram, C Wren, M Bhate, P Robertson, S Hunter 289

GENETIC EVIDENCE THAT MUTATIONS IN THE *COL1A1, COL1A2, COL3A1,* OR *COL5A2* COLLAGEN GENES ARE NOT RESPONSIBLE FOR MITRAL VALVE PROLAPSE
A M Henney, P Tsipouras, R C Schwartz, A H Child, R B Devereux, G J Leech 292

GENETIC SEGREGATION ANALYSIS OF FAMILIAL MITRAL VALVE PROLAPSE SHOWS NO LINKAGE TO FIBRILLAR COLLAGEN GENES P Wordsworth, D Ogilvie, F Akhras, G Jackson, B Sykes 300

CASE REPORT

ACUTE MYOCARDIAL INFARCTION IN INFANCY: UNMASKING OF ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY BY LIGATION OF AN ARTERIAL DUCT
N Sreeram, S Hunter, C Wren 307

NOTICES 308

Number 4

REVIEW: DOES THE ATRIOVENTRICULAR NODE CONDUCT? F L Meijler, C Fisch 309

A DOUBLE BLIND PLACEBO CONTROLLED STUDY OF EARLY AND LATE ADMINISTRATION OF RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR IN ACUTE MYOCARDIAL INFARCTION
A J McNeill, S R Cunningham, D J Flannery, G W N Dalzell, C M Wilson, N P S Campbell, M M Khan, G C Patterson, S W Webb, A A J Adgey 316

IMPACT OF A POLICY OF DIRECT ADMISSION TO A CORONARY CARE UNIT ON USE OF THROMBOLYTIC TREATMENT J M A Burns, K J Hogg, A P Rae, W S Hillis, F G Dunn 322

USE OF A HOLLOW WIRE TO FACILITATE ANGIOPLASTY OF OCCLUDED VESSELS
L D R Smith, D Katritsis, M M Webb-Peploe 326

EFFECT OF FLOSEQUINAN ON EXERCISE CAPACITY AND SYMPTOMS IN SEVERE HEART FAILURE
J S Elborn, C F Stanford, D P Nicholls 331

HALF TIME OF THE DIASTOLIC AORTOVENTRICULAR PRESSURE DIFFERENCE BY CONTINUOUS WAVE DOPPLER ULTRASOUND: A MEASURE OF THE SEVERITY OF AORTIC REGURGITATION?
S O Samstad, L Hegrenaes, T Skjaerpe, L Hatle 336

TRANSMITRAL VELOCITIES MEASURED BY PULSED DOPPLER IN HEALTHY VOLUNTEERS: EFFECTS OF ACUTE CHANGES IN BLOOD PRESSURE AND HEART RATE
S A Smith, J E Stoner, A E Russell, J M Sheppard, P E Aylward 344

ISOPRENALINE AS AN AID TO THE INDUCTION OF CATECHOLAMINE DEPENDENT SUPRAVENTRICULAR TACHYCARDIAS DURING PROGRAMMED STIMULATION
B Brembilla-Perrot, A Terrier de la Chaise, M Pichené, E Aliot, F Cherrier, C Pernot 348

ENDOCARDITIS IN INTRAVENOUS DRUG ABUSERS WITH STAPHYLOCOCCAL SEPTICAEMIA
J M A Burns, K J Hogg, W S Hillis, F G Dunn 356

AORTIC VALVOTOMY FOR CRITICAL AORTIC STENOSIS IN NEONATES AND INFANTS AGED LESS THAN ONE YEAR S Balaji, B R Keeton, G R Sutherland, D F Shore, J L Monro 358

DIAGONAL EARLOBE CREASES AND FATAL CARDIOVASCULAR DISEASE: A NECROPSY STUDY N Kirkham, T Murrells, D H Melcher, E A Morrison 361

CASE REPORTS

PERINATAL MANAGEMENT OF CRITICAL AORTIC VALVE STENOSIS DIAGNOSED BY FETAL ECHOCARDIOGRAPHY M A Robertson, P J Byrne, P A Penkoske 365

WOLFF-PARKINSON-WHITE SYNDROME AFTER TRANSPLANTATION OF THE HEART J-J Goy, L Kappenberger, M Turina 368

SERIAL ANGIOGRAPHIC FINDINGS DURING THE DEVELOPMENT OF A SACCULAR ANEURYSM OF THE CORONARY ARTERY IN ASSOCIATION WITH UNSTABLE ANGINA J Goudevenos, M Been, D Williams 372

UNRUPTURED ANEURYSM OF THE SINUS OF VALSALVA PRESENTING WITH ISOLATED HEART BLOCK: ECHOCARDIOGRAPHIC DIAGNOSIS AND SUCCESSFUL SURGICAL REPAIR R A S Ahmad, S Sturman, R D S Watson 375

PROPRANOLOL INDUCED BRADYCARDIA IN TETRALOGY OF FALLOT D J Clark, K C Chan, J L Gibbs 378

NOTICES 380

Number 5

EDITORIAL: SUCCESSFUL AND UNSUCCESSFUL CORONARY THROMBOLYSIS M J Davies 381

CINEANGIOGRAPHIC AND PATHOLOGICAL FEATURES OF THE INFARCT RELATED VESSEL IN SUCCESSFUL AND UNSUCCESSFUL THROMBOLYSIS T Onodera, H Fujiwara, M Tanaka, D-J Wu, M Matsuda, G Takemura, M Ishida, A Kawamura, C Kawai 385

PATHOLOGICAL CHANGES AFTER INTRAVENOUS STREPTOKINASE TREATMENT IN EIGHT PATIENTS WITH ACUTE MYOCARDIAL INFARCTION S G Richardson, D C Allen, P Morton, J G Murtagh, M E Scott, D B O'Keeffe 390

FAVOURABLE LONG TERM PROGNOSIS IN PATIENTS WITH NON-Q WAVE ACUTE MYOCARDIAL INFARCTION NOT ASSOCIATED WITH SPECIFIC ELECTROCARDIOGRAPHIC CHANGES W E Boden, R E Kleiger, R S Gibson, B R Reddy, K B Schechtman, D J Schwartz, R J Capone, R Roberts, and the Diltiazem Reinfarction Study Research Group 396

RISK FACTORS FOR STROKE AND MYOCARDIAL INFARCTION IN WOMEN IN THE UNITED KINGDOM AS ASSESSED IN GENERAL PRACTICE: A CASE-CONTROL STUDY S G Thompson, G Greenberg, T W Meade 403

PROGNOSTIC SIGNIFICANCE OF PROGRAMMED VENTRICULAR STIMULATION IN SURVIVORS OF ACUTE MYOCARDIAL INFARCTION A K Bhandari, R Hong, A Kotlewski, N McIntosh, P Au, A Sankoorikal, S H Rahimtoola 410

PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY OF LEFT INTERNAL MAMMARY ARTERY GRAFTS: TWO YEARS' EXPERIENCE WITH A FEMORAL APPROACH M R Bell, D R Holmes Jr, R E Vlietstra, D R Bresnahan 417

A NEW EXERCISE TEST FOR THE ASSESSMENT OF HEART FAILURE: USE OF A SELF POWERED TREADMILL J Parameshwar, J-H E Dambrink, J Sparrow, C Wright, A Park, J Tweed, P A Poole-Wilson 421

EFFECT OF TEMPERATURE ON RATE OF LEFT VENTRICULAR PRESSURE FALL IN HUMANS R A Luke, C E Gillbe, R S Bonser, M Paneth, D Somerset, J Thomas, D G Gibson 426

BALLOON DILATATION OF STENOSED BLALOCK-TAUSSIG SHUNTS S A Qureshi, R P Martin, D F Dickinson, S Hunter 432

PROCEEDINGS OF THE BRITISH CARDIAC SOCIETY 435

CORRESPONDENCE 483

NOTICES 484

CORRECTION: CARDIAC SURGERY FOR PATIENTS AGED 65 YEARS AND OLDER: A LONG TERM SURVIVAL ANALYSIS S Livesey, N Caine, D J Spiegelhalter, T A H English, J Wallwork 484

Number 6

OUTCOME IN PATIENTS WITH RECURRENT RESTENOSIS AFTER PERCUTANEOUS TRANSLUMINAL BALLOON ANGIOPLASTY J J Glazier, T R Varricchione, T J Ryan, N A Ruocco, A K Jacobs, D P Faxon 485

ELECTROCARDIOGRAPHIC EVIDENCE OF MYOCARDIAL SALVAGE AFTER THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION H J Hogg, K R Lees, R S Hornung, C A Howie, F G Dunn, W S Hillis 489

SILENT MYOCARDIAL ISCHAEMIA IN PATIENTS REFERRED FOR CORONARY BYPASS SURGERY BECAUSE OF ANGINA: A COMPARISON WITH PATIENTS WHOSE SYMPTOMS WERE WELL CONTROLLED ON MEDICAL TREATMENT D Mulcahy, J Keegan, D Lindsay, J Sparrow, A Park, C Wright, K Fox 496

INITIAL EXPERIENCE WITH A MICROPROCESSOR CONTROLLED CURRENT BASED DEFIBRILLATOR G W N Dalzell, S R Cunningham, J Anderson, A A J Adgey 502

CENTRAL HAEMODYNAMIC CHANGES AFTER A MEAL H Kelbæk, O Munck, N J Christensen, J Godtfredsen 506

THE QT INTERVAL IN ATRIAL FIBRILLATION G R Pai, J M Rawles 510

RIGHT VENTRICULAR INFARCTION: DIAGNOSTIC ACCURACY OF ELECTROCARDIOGRAPHIC RIGHT CHEST LEADS V3R TO V7R INVESTIGATED PROSPECTIVELY IN 43 CONSECUTIVE FATAL CASES FROM A CORONARY CARE UNIT H R Andersen, E Falk, D Nielsen 514

COLD INTOLERANCE IN PATIENTS WITH ANGINA PECTORIS: EFFECT OF NIFEDIPINE AND PROPRANOLOL I Peart, R E Bullock, C Albers, R J C Hall 521

CLINICAL, HAEMODYNAMIC, AND PHARMACOLOGICAL EFFECTS OF WITHDRAWAL AND REINTRODUCTION OF DIGOXIN IN PATIENTS WITH HEART FAILURE IN SINUS RHYTHM AFTER LONG TERM TREATMENT S E Pugh, N J White, J K Aronson, D G Grahame-Smith, J G Bloomfield 529

ANOMALOUS SUBAORTIC POSITION OF THE BRACHIOCEPHALIC (INNOMINATE) VEIN: A REVIEW OF PUBLISHED REPORTS AND REPORT OF THREE NEW CASES L M Gerlis, S Y Ho 540

CASE REPORTS

INJURY TO A SAPHENOUS VEIN GRAFT DURING REMOVAL OF A TEMPORARY EPICARDIAL PACING WIRE ELECTRODE C Price, D J M Keenan 546

SEVERE HAEMOLYSIS AFTER PERCUTANEOUS CLOSURE OF A DUCTUS ARTERIOSUS (ARTERIAL DUCT) E J Ladusans, I Murdoch, J Franciosi 548

PERCUTANEOUS TRANSLUMINAL BALLOON DILATATION OF THE MITRAL VALVE IN PREGNANCY R Smith, D Brender, M McCredie 551

NOTICES 553

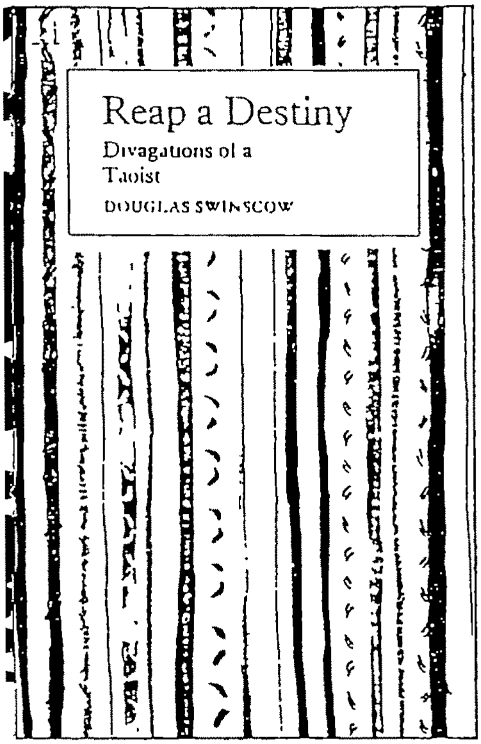
CORRESPONDENCE 554

LIST OF ADVISERS 555

INDEX 557

The BMJ's series of books of general interest by medical writers

The
MEMOIR
Club



To readers of the *BMJ* Douglas (Dougal) Swinscow is probably best known as its former deputy editor and author of one of its most popular books, *Statistics at Square One.* But he is also a world authority on lichens, and his first work to appear in print was a poem, published by T S Eliot in the *New English Weekly*. A lover of the arts and a painstaking scientist, a philosopher who nevertheless thrived in a military role and went through one of the bloodiest battles of the second world war (at Arnhem), Douglas Swinscow looks back at the contrasting forces that have shaped his life and at the personal choices that have gone into the making of his character.

Price: Inland £14.95; Abroad £17 50
BMA members: Inland £13.95; Abroad £16.50
ncluding postage, by air abroad

ORDER FORM

BRITISH MEDICAL JOURNAL
PO BOX 295, LONDON WC1H 9TE
or any leading medical bookseller

Please send me

	UK	ABROAD
☐ **Reap a Destiny** by Douglas Swinscow	£14 95	£17.50
☐ **Blood, Sweat, and Cheers** by Sir Ian Fraser	£14 95	£17 50
☐ **A Natural History of Everyday Life** by Lord Taylor of Harlow	£19 95	£24 00
☐ **Portraits from Memory** by Sir James Howie	£14 95	£17 50
☐ **Not Always on the Level** by E J Moran Campbell	£14.95	£18.50
☐ **Recollections and Reflections** by Sir Douglas Black	£14 95	£17 50
☐ **Doctors in Science and Society** by Sir Christopher Booth	£14.95	£19.50
BMA members please deduct from the price of Memoir Club books	£1 00	£1 00

NAME ....
Please print name and address clearly

ADDRESS ....

....

....

I enclose ....

BMA Membership No ....

Please make cheques payable to **British Medical Journal** or debit my credit card *(please tick box)*

☐ Access/MasterCard ☐ Barclaycard/Visa ☐ American Express

Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Card expiry date ....

Signature ....

☐ Please send me a book catalogue

Easy, one touch control of hypertension right from the start

SEP 1989

Right from the start 'Tenormin' LS gives you easy and effective control of mild to moderate hypertension. For you and the majority of your patients that means no juggling of doses or unnecessary repeat visits. And with 'Tenormin' LS being well tolerated by the majority of patients, what could be easier?

'TENORMIN' LS

DOSAGE

HYPERTENSION

'Tenormin' LS – 50 mg atenolol orally once a day; some patients may respond adequately to 'Tenormin' low strength (LS). If response is inadequate, increase to two tablets daily taken orally as a single dose.

ANGINA PROPHYLAXIS

'Tenormin' LS – 50 mg atenolol. Two tablets orally in single or divided doses.

CHILDREN – 'Tenormin' LS is not recommended for use in children.

ELDERLY PATIENTS – Dosage requirements for 'Tenormin' LS may be lower, especially in patients with renal impairment.

CONTRA-INDICATIONS

Heart block, cardiogenic shock.

PRECAUTIONS

Untreated cardiac failure, bradycardia, renal failure, anaesthesia, pregnancy. Caution in patients with chronic obstructive airways disease or asthma. Atenolol modifies the tachycardia of hypoglycaemia. Co-administration with verapamil or Class I antidysrhythmic agents. Withdrawal of clonidine. Withdrawal of beta blocking drugs should be gradual in patients with ischaemic heart disease.

SIDE-EFFECTS

Coldness of extremities, bradycardia and muscular fatigue may occur. Sleep disturbance rarely seen. Rashes and dry eyes have been reported with beta blockers – consider discontinuance if they occur.

PRODUCT LICENCE NUMBER AND BASIC NHS COST

'Tenormin' LS Tablets 29/0086 in calendar packs of 28, £5.49.

'Tenormin' LS is a trade mark.

Further information is available on request from the Company.

TENORMIN LS

atenolol 50 mg

Easy control, simple success right from the start

STUART

Stuart Pharmaceuticals Limited
Stuart House, 50 Alderley Road,
Wilmslow, Cheshire SK9 1RE

In Support of Science. . .

Official Journals of the American Heart Association

Circulation

Burton E. Sobel, M.D., Editor
ISSN: 0009-7322
Devoted to clinical research and advances in the cardiovascular field. Original articles of cardiovascular clinical and laboratory investigations, including pathophysiology and natural history, diagnostic methods, therapy and prevention. Editorials, Perspectives, Preludes and Progress, AHA News. Monthly.

Circulation Research

Harry A. Fozzard, M.D., Editor
ISSN: 0009-7330
Concerned with basic cardiovascular research. Original articles and editorials for clinicians interested in basic science and for research workers in anatomy, biology, biochemistry, biophysics, microbiology, physiology, pharmacology, and pathology, as well as experimental medicine. Brief Reviews, Brief Communications, Letters to the Editor, AHA News. Monthly.

Hypertension

Edgar Haber, M.D., Editor
ISSN: 0194-911X
Publishes reports of clinical and laboratory investigations in hypertension. Designed for clinicians, clinical investigators, laboratory scientists. Original Investigations, Brief Reviews, Symposia, Case Reports, AHA News. Monthly.

Stroke

A Journal of Cerebral Circulation

Oscar M. Reinmuth, M.D., Editor
ISSN: 0039-2499
Of interest to the practicing physician — especially the internist, cardiologist and neurologist — as well as teacher, clinical investigator, laboratory scientist, and student. Articles deal with prevention, diagnosis, treatment and rehabilitation. Progress Reviews, Original Contributions, Short Communications, Abstracts of Literature, Comments, Opinions, and Reviews, Letters to the Editor, AHA News. Monthly.

Arteriosclerosis

A Journal of Vascular Biology and Thrombosis

Edwin L. Bierman, M.D., Editor
ISSN: 0276-5047
Includes original research papers and state-of-the-art reviews from a variety of disciplines bearing on the biology, prevention, and impact of vascular diseases relating to arteriosclerosis. Designed for physicians and investigators. Original Contributions, Editorials, Reviews, Meeting Summaries, Special Reports, AHA News, Bimonthly.

Recurring Bibliography of Hypertension

ISSN: 0090-1326
Published by the AHA in cooperation with the National Library of Medicine. Provides a rapid survey of current published developments in the field of hypertension. Bimonthly.

American Heart Association
National Center
Scientific Publications
7320 Greenville Avenue
Dallas, Texas 75231

For rate and order information:

Japan, contact:
Nankodo Co., Ltd.
42-6 Hongo 3-chome
Bunkyo-ku, Tokyo 113
JAPAN

Europe, contact:
Harcourt-Brace-Javonovich
Foots Cray High Street
Sidcup
Kent DA14 5HP, ENGLAND

Published by British Medical Association, Tavistock Square, London WC1H 9JR
and printed in England by Eyre & Spottiswoode Ltd. London and Margate.